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es James Fox, M.D.
ORD, CONN.

TRANSACTIONS OF THE

# SECTION ON

# Practice of Medicine

of the
American Medical Association
at the Sixty-Second Annual
Session, held at Los Angeles,
Cal., June 27 to 30, 1911

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# LIST OF OFFICERS

Those named below have served as officers in this Section. This Section has included other subjects in the earlier years, as will be seen by the headings which denote the different Section titles. The names of the officers have been taken from the published records, which are deficient in some cases. It will be appreciated if any additional data are brought to the attention of the Secretary of the American Medical Association.

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# PROCEEDINGS OF THE SESSION

TUESDAY, JUNE 27—AFTERNOON

The meeting was called to order at 2:15 p. m., in the Majestic Theater, by the Chairman, Dr. Allen A. Jones, Buffalo.

Dr. H. A. Giltner, U. S. N., read a paper on "Verruca Peruana or Carrion's Disease." No discussion.

Dr. C. M. Richter, San Francisco, read a paper on "The Epidemiology of Pneumonia." No discussion.

Drs. Walter Brem and F. C. Watson, Cristobal, Canal Zone, presented a paper on "Successful Treatment of a Typhoid Bacillus-Carrier by Vaccination." Discussed by Drs. Frank Billings, Percy M. Ashburn, William Litterer and Walter Brem.

Dr. F. M. Pottenger, Monrovia, Cal., read a paper on "Causation and Treatment of Fever in Tuberculosis." Discussed by Drs. Edward F. Wells, Norman Bridge, Frank Billings, Philip King Brown, C. F. Tenney and F. M. Pottenger.

Dr. Norman Bridge, Los Angeles, read a paper on "Streptothrix (Actinomycosis) of the Lungs." No discussion.

Dr. N. W. Jones, Portland, Ore., read a paper on "Hemorrhagic Erosions of the Stomach." Discussed by Drs. Robert T. Morris, J. F. Hultgen, Philip King Brown and N. W. Jones.

Dr. W. J. Butler, Chicago, read a paper on "Immuno-Diagnostics in Internal Medicine." Discussed by Drs. F. M. Pottenger and W. J. Butler.

The Chairman: I wish at this time to interrupt the proceedings for a short time to announce the Nominating Committee: On this committee, I will appoint the following: Drs. W. Jarvis Barlow, Los Angeles; Henry B. Favill, Chicago, and Alexander Lambert, New York. Because of the absence of Dr. Joseph Miller, who serves on the Executive Committee, I will appoint in his place Dr. Herbert Moffit, San Francisco.

Dr. J. F. Hultgen, Chicago, read a paper on "The Leukocytology of Typhoid and Paratyphoid Fevers." No discussion.

WEDNESDAY, JUNE 28—MORNING

Dr. W. Jarvis Barlow, Los Angeles, read a paper on "Effects on Secondary Anemia by Hypodermic Injections." Discussed by Drs. Alexander Lambert, Bonnell, Samuel D. Swope, Dudley Fulton and W. Jarvis Barlow.

Dr. Edward F. Wells, Chicago, read a paper on "Reserve Renal Capacity in Chronic Interstitial Nephritis." Discussed by Drs. Frank Billings, Alexander Lambert, W. L. Bierring and Edward F. Wells.

Dr. Roger I. Lee, Boston, read a paper on "Pathologic Findings in Hypertension." Discussed by Drs. William Ophuls, Edward F. Wells, Frank Billings, C. F. Hoover, Charles L. Greene, W. L. Bierring, Percy M. Ashburn and Roger I. Lee.

Dr. Charles L. Greene, St. Paul, Minn., read a paper on "New Clinical Values in the Treatment of the Gastric Neuroses." Discussed by Drs. Walter B. Cannon, Frank Billings, W. J. Butler, Seale Harris and Charles L. Greene.

Dr. Alexander Lambert, New York, read a paper on "The Blood-Pressure in Pneumonia." Discussed by Drs. Dudley Fulton, Wilder Tileston, Percy M. Ashburn and Alexander Lambert.

Drs. H. D. Arnold and R. C. Larrabee, Boston, presented a paper on "The Importance of the Quantitative Regulation of Diet." Discussed by Dr. Wilder Tileston.

Drs. J. M. Anders and A. C. Morgan, Philadelphia, presented a paper on "Pleurisy and Empyema in Pneumonia." Discussed by Drs. J. N. Hall, Everett J. Brown, C. F. Hoover and A. C. Morgan.

### Wednesday, June 28—Afternoon

Symposium on Syphilis.

Dr. L. S. Schmitt, San Francisco, read a paper on "Laboratory Diagnosis of Syphilis."

Dr. Frank Billings, Chicago, read a paper on "Visceral Syphilis."

Dr. Albert Keidel, Baltimore, read a paper on "Value of the Wassermann Reaction and of Salvarsan."

Dr. D. W. Montgomery, San Francisco, read a paper on "Disadvantages Incident to the Administration of Salvarsan."

Dr. W. T. Wootton, Hot Springs, Ark., read a paper on "Adequate Treatment of Syphilis."

These five papers were discussed by Drs. Howard Fox, W. J. Butler, C. F. Hoover, Harry Reeves Olliver, Harvey G. Parker, William Litterer, G. H. Aiken, John H. Graves, William W. Graves, B. H. Orndorff, Percy M. Ashburn, H. S. Plummer, L. S. Schmitt, Frank Billings, D. W. Montgomery and W. T. Wootton.

### Thursday, June 29—Morning

Dr. A. J. Hodgson, Waukesha, Wis., read a paper on "Treatment of Diabetes." Discussed by Drs. Robert T. Morris,

Edward F. Wells, H. B. Favill, Wernigk, A. J. Ochsner and A. J. Hodgson.

Dr. G. W. McCoy, San Francisco, read a paper on "Bubonic Plague with Special Reference to that of Ground-Squirrel Origin." Discussed by Drs. Edward F. Wells and G. W McCoy.

Dr. H. S. Plummer, Rochester, Minn., read a paper on "Relation of the Symptomatology and Pathology to Operative Mortality in Exophthalmic Goiter." Discussed by Drs. C. H. Mayo, Martin B. Tinker and H. S. Plummer.

Dr. W. E. Musgrave, Manila, P. I., read a paper on "Treatment of Intestinal Amebiasis." Discussed by Drs. Walter Brem, Percy M. Ashburn, Louis B. Wilson and W. E. Musgrave.

Dr. J. W. Draper, Rochester, Minn., read a paper on "Experimental Work on Intestinal Auto-Intoxication." Discussed by Dr. W. T. Councilman.

Report of the Nominating Committee. Dr. Alexander Lambert made this report: Chairman, Dr. Wilder Tileston, New Haven, Conn.; Vice-Chairman, Dr. Walter L. Bierring, Des Moines, Ia.; Secretary, Dr. Roger S. Morris, Baltimore; Orator, Dr. Charles L. Greene, St. Paul, Minn.; Delegate, Dr. J. A. Capps, Chicago, and Alternate Delegate, Dr. S. W. S. Toms, Nyack, New York.

Dr. Lambert: I move that the action on this report be deferred until after the orator's address this afternoon when a larger number of members will be present. Seconded. Carried.

Drs. G. R. Satterlee and L. T. Le Wald, New York, presented a paper on 'Some Obscure Conditions of the Digestive Tract as Studied by the Roentgen Ray." No discussion.

Drs. W. T. Councilman and C. H. Dunn, Boston, presented a paper on "Myatonia Congenita (Oppenheim); Report of a Case with Autopsy." No discussion.

THURSDAY, JUNE 29—AFTERNOON

Dr. C. F. Hoover, Cleveland, delivered the Oration in Medicine: "A Clinical Study of Disturbances in Rate and Rhythm of Respiration." Discussed by Dr. Henderson.

It was moved and seconded that the report of the Nominating Committee be adopted. Unanimously carried.

Dr. A. W. Hewlett, Ann Arbor, Mich., read a paper on "Infantilism with Disease of the Pituitary Gland." No discussion.

Dr. Dudley Fulton, Los Angeles, read a paper on "A Clinical Study of the Mobility of the Heart." No discussion.

The following papers were read at a Symposium on Poliomyelitis—a joint session with the Section on Diseases of Children.

Drs. Samuel G. Dixon, Harrisburg, Pa., and H. T. Karsner, Philadelphia, presented a paper on "Epidemiologic and Etiologic Studies of Acute Poliomyelitis in Pennsylvania."

Drs. R. W. Lovett and M. W. Richardson, Boston, presented a paper on "Infantile Paralysis."

These two papers were discussed by Dr. Philip King Brown.

# STREPTOTHRICOSIS (ACTINOMYCOSIS) OF THE LUNGS

NORMAN BRIDGE, M.D.
LOS ANGELES

In 1908 I reported[1] seven cases of what I believed to be pulmonary actinomycosis (streptothricosis) discovered in one year. Since then several additional cases have been encountered. They have all been infested by a streptothrix which I have supposed to be the *Streptothrix actinomyces*. Some of these patients have also had tuberculosis, death resulting in each case; some have had simple streptothricosis; several of these have recovered.

Of the former series three patients had also pulmonary tuberculosis and all were free from infection in other parts of the body. In one case (No. 2, N., of the mixed disease) the patient, who had a marked lesion of the left lung, had died April, 1908, after a year's struggle and eight months after coming under observation.

In another mixed case (No. 3, G.) the patient survived till March, 1909. In this case there was little involvement of the lungs, the apices only being invaded, especially the right. The larynx was profoundly involved, with much swelling, swallowing being difficult and painful, and aphonia being absolute for many months before death.

CASE 1.—The patient, A., was reported probably cured, had remained so to a recent date, the recovery apparently being permanent. This was the most marked and characteristic case of the series, almost the whole of the left lung being more or less diseased, the patient having expectorated large quantities

1. Tr. Sect. Hyg. San. Sc., A. M. A., 1908, p. 242.

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of bloody malodorous muco-pus for many weeks, often a pint or more in twenty-four hours, and recovering with a mass of consolidated tissue in the left upper third, with reduced vesicular murmur and bronchial breathing over the whole lung.

CASE 4.—The patient absconded and has not been rediscovered.

CASE 5.—The patient had mixed disease, went east and his fate is unknown.

CASE 6.—M., the patient, seemed to pass into recovery with a rather marked consolidation in the bottom of the left lung posteriorly, and a lesser one in the right apex. Marked fibrosis occurred, especially in the left side, which greatly reduced the motion of the chest-walls—in fact, nearly abolished it; the breathing was mostly abdominal, and even moderate exertion caused extreme dyspnea. Yet the man looked well and, barring the short-windedness, felt so. A few actinomyces were found in his expectoration after the first report, but none for several months before his death—indeed, for many weeks there had been no expectoration of pus. The man went to Colorado in 1909, was seized with some complication and died in two or three days.

CASE 7.—W., the patient, had a marked lesion in the lower left chest posteriorly, with free expectoration of thick bloody sputum (his case having been early taken for one of some extraordinary pneumonia—as indeed it was), completely recovered, with evidence of moderate thickening of tissue (so-called consolidation) in the region involved. His health is apparently perfect.

CASE 8.—Of the second series of cases, the first was a mixed one, the patient (B.) being a bachelor, aged 25, a lawyer. He came under observation late in July, 1908, and had then been sick for fifteen months. At first his expectoration was bloody; for a year it had not been over a half ounce in twenty-four hours, and blood-free. The lesion was a diffused and moderate one throughout the left lung. It gradually grew worse, with more and more signs of consolidation; dulness, reduced motion, bronchial breathing, râles, reduced vesicular murmur, especially at the bottom of the lower lobe, and finally a cavity. He failed and died in April, 1910. Both tubercle bacilli and actinomyces were found in the expectoration and were distinct and typical.

CASE 9.—R., the patient, is a vigorous-looking bachelor, a street-car conductor of 28 years. He was first seen in December, 1908. He felt poorly and coughed for several months. Expectoration had been moderate in amount and occasionally bloody. A few actinomyces were found but no tubercle bacilli.

There was almost an entire absence of physical signs, barely slight bronchial breathing in the right apex. The germs have increased in the sputa. There has been little or no fever, and he keeps his weight and general condition; the daily expectoration is about three ounces, and it is occasionally bloody, and fetid. Early in 1910 his nose apex swelled, got red and finally broke down in ulceration of the skin in numerous small points. The streptothrix was found in the discharges from the ulcers. The condition recovered under tincture of iodin locally and iodin internally. Later a similar ulceration occurred on one of his legs above the ankle and healed.

CASE 10.—H., the patient, of Wyoming, came under observation March 22, 1909. He is a sheep raiser, 52 years of age, married. The previous autumn he had what was pronounced left pneumonia and was in bed four or five days. He was expectorating 8 ounces of pinkish muco-pus every twenty-four hours; had no fever, but was very short-winded; he had lost 15 pounds in weight. The expectoration teemed with actinomyces. He had manifestly extensive effusion in the left pleural cavity which was aspirated March 25 of the amount of 20 ounces of pinkish sero-pus containing what appeared to be debris of actinomyces. March 31, the left side remaining still flat, a drainage-tube was inserted which promptly discharged 30 ounces of fluid. There was no lesion of the right lung, so the expectoration manifestly came from the upper part of the left lung and may in part have come through a perforation from the pleural cavity, since after the drainage the expectoration was reduced markedly. The patient soon returned home and his doctor reported for a time a moderate improvement. He returned to Los Angeles in the winter of 1909-10. Actinomyces in fragments were still found in the discharges. An operation for removal of sections of ribs was done after his return home in the spring of 1910.

CASE 11.—C., the patient, was in the practice of my associate, Dr. George L. Cole, with a record as follows: He had come under observation December 3, 1908. He was a lumberman, 62 years of age, had been well since 1870 until eight or ten months before; then a cough began and there was pain in the left chest. He was put to bed by his previous physician during January and February, 1908, having been aspirated four times up to April of that year. About one quart of fluid was procured each time.

His pulse was weak and cough bad (Dec. 3, 1908), although expectoration was trifling. Dr. Cole found complete dulness over the left chest, the heart being pushed to the right; the apex-beat was distinctly to the right of the sternum. The patient was aspirated of between 3 and 4 quarts of bloody

fluid; but the little expectoration that was procured contained actinomyces. Jan. 29, 1909, the left side was still profoundly dull throughout. There was tactile fremitus down to the fifth rib, also voice sounds. The heart apex was under the sternum. This was substantially the condition April 23, 1909. There was no real vesicular murmur even at the apex. There was no fever; pulse and respiration were rapid. The weight had decreased 24 pounds. Yet, the patient was about, attending to business daily and looked like a man only slightly under normal vigor. He grew gradually worse and died Nov. 4, 1909. The left lung was found compressed into the size of a large human fist. The right lung had become extensively invaded, at the apex, by what the microscope showed to be carcinoma.

CASE 12.—C., the patient, is a single woman aged 40, who has had tuberculosis and has been coughing more or less for a number of years. She has also had a great deal of nervous debility. Her previous physicians found tubercle bacilli on several occasions.

On my examination made in 1908 her right lung had slightly reduced motion, marked reduction in vesicular murmur, trifling dulness and sharp bronchial breathing at the top, reduced fremitus over the middle and lower portions, trifling bronchial breathing at the top of the left lung. The patient was not expectorating much and it was impossible to procure a good sputum specimen. Her temperature was 1 degree above normal. Hers was regarded as an arrested case of tuberculosis.

After an absence of a year she returned for another examination. She had recently been having fever—to 102 F.—with wheezing, cough and poor appetite. There was now marked consolidation of the lower part of the right lung posteriorly and about the same condition as before in the upper portion. No tubercle bacilli were present in the sputum, but numerous actinomyces.

The patient had not lost much in weight and her general functions were fairly normal. She had been in very fair health the previous year, except for some irregularities in menstruation. She soon ceased to have fever. The thickening at the base of the right lung disappeared and general improvement was noticeable. Occasionally she had a recurrence of slight fever, with numerous râles throughout the right lung. It was evident that the infection was in the right apex. The actinomyces mostly disappeared after a few months, and her general health was greatly improved, when she suddenly developed a rather marked case of exophthalmic goiter. This

improved after a few months. She is now in fair health, but recently a few actinomyces were found.

CASE 13.—C., a man of 40, widower, an office man from Philadelphia, came under observation May, 1909. His general health was good; his appearance was that of a well man; his general functions as to digestion and general vigor were normal. He had no fever and probably had had none. He had been hoarse more or less for six months and had had a cough with a small amount of expectoration of a thin purulent character, with occasional streaks of blood. The hoarseness was worse in the mornings, better evenings. There had been no difficulty or pain in swallowing. He was only slightly short-winded.

His eastern physicians had repeatedly searched his expectoration for tubercle bacilli and had failed to find any, and one of them had searched for the germs supposed to belong to syphilis, with negative results. He had received free doses of potassium iodid from the last-mentioned physician, who regarded the case as syphilitic (although the patient denied the possibility of it) and reported improvement for a time under the treatment. The patient confirmed this last statement.

Physical examination of the chest (May, 1909) revealed absence of dulness and râles; the slightest possible reduction of vesicular murmur over the upper left chest, and a sort of loud bronchial breathing over both apices, of a character suggesting tracheal narrowing. The larynx was extensively diseased; all the tissues were swollen; the epiglottis was swollen, ulcerous, and cleft rather deeply in its center longitudinally; the vocal cords were swollen and red, and the false cords and arytenoid regions were large and red but apparently not ulcerous. It was impossible to get a good view of the vocal cords and the lining of the trachea. There were two white ulcerous patches on the front of the left half of the soft palate. The sputum contained a few streptococci and many actinomyces of a typical appearance but no tubercle bacilli.

The patient was advised to have his throat sprayed with an 8 grain water solution of sulphate of copper, and to take ⅓ grain of the copper drug and 6 grains of sajodin, three times a day. He soon disappeared and was not seen again. He died in February, 1910.

CASE 14.—T., a married woman, aged 50, was first seen in February, 1909. She had a laparotomy some months previously for gall-bladder symptoms, followed by some amelioration. She had all the physical signs of a moderate infiltration of what appeared to be tuberculosis of the right apex anteri-

orly. She had slight fever, moderate expectoration and general debility. No tubercle bacilli were found after repeated examinations, and no actinomyces until June 10, when a single granule was discovered. Afterward, numerous typical ones were found, some of them in clumps. Later, bloody expectoration in small quantity appeared for a short time with extension of dulness and reduced vesicular murmur in the back of the right apex down to the upper part of the central third of the lung. Fever increased with this extension of the disease. The fever subsided simultaneously with the discharge of larger masses of the peculiar germs. This cycle was repeated several times during the year; extension of the disease and fever, the latter subsiding on the discharge of a large mass of bloody pus with terrible odor. The patient died in 1910. The post-mortem findings are reported below. This case occurred in the house of one of the cured patients reported above.

CASE 15.—D., a widow, 65 years of age, had had a moderate cough for a year or more, with a little daily yellow expectoration. In 1908 I found slight physical signs of thickening in the right lung apex. The general health was good for a person of her age. She was a large woman and had lost little weight; she had been substantially without fever. Early in October, 1909, she had had a slight pulmonary hemorrhage and continued to expectorate blood-flecked and odorless sputa for several weeks. No other symptoms occurred. Repeated examinations of her sputa failed to find either tubercle bacilli or actinomyces, until after this hemorrhage. Then the ray specimens were found in small numbers, but no tubercle bacilli. Early in December, 1909, she was seized with a flooding pulmonary hemorrhage and died in a few minutes. No necropsy was made.

CASE 16.—F., an unmarried man aged 26, a clerk in a chemical and apparatus supply house in Los Angeles for some years, had had cough for several months with a little odorless expectoration, and has lost a few pounds in weight. He has felt a sense of general debility, but has kept at work. There has been less than 1 degree elevation of temperature in the afternoons. Slight dulness, an occasional râle and moderate bronchial breathing have been found at the right apex. Characteristic actinomyces were found but no tubercle bacilli.

CASE 17.—The patient, Br., in the practice of Dr. Robert Moody of the University of California, at Berkeley, was a single woman, a teacher, 40 years old, with extreme lateral curvature of the spine. Her father had had asthma fifteen years and died of heart disease; one brother died of tuberculosis. The patient had pleurisy in 1903, and the next year,

tuberculosis of the right lung. Dr. Moody first saw her in January, 1908. There was a cavity in the right lung; tubercle bacilli and actinomyces were found in the sputum. Tuberculin was given (1/500 to 1/1000 mg. weekly) till May, 1910, when the tubercle germs disappeared. Streptothrix germs have persisted and the patient was still living a few weeks ago.

The treatment of these cases has been tonic and regulation of functions with iodin in some form and frequently sulphate of copper. The latter was given in doses of ⅓ gr. three times a day when the stomach could bear it, and the iodin in the form of iodid of potassium, or of sodium, and sajodin.

The cases here reported emphasize the fact that pulmonary streptothricosis is not so very uncommon; that most physicians can discover examples if they will only look for them, and that it must be true that a large proportion of the cases of so-called non-tuberculous phthisis are instances of pulmonary streptothricosis of some variety. The number of cases of this sort is considerable and most general practitioners have encountered them and have been puzzled by them.

This whole series proves that it is futile to try to connect the cases with the disease in cattle or in other people. Patient 1 was a farmer, but denied ever having seen a case of lumpy jaw. Patient 3 was a lawyer who took milk from a dairy found to contain some cows afflicted with tuberculosis and fewer cows afflicted with lumpy jaw. The other cases were free of any suggestion as to such an origin of the disease. Case 14 is the only one that appears to have been connected with any other case.

The patients mostly came from widely separated parts of the country and had no connection with each other. Nor was a single case of the lung affection secondary to a lesion elsewhere in the body, and in no instance has the disease appeared secondarily in other organs than the lungs and pleura, save Case 9, in which the skin became involved and recovered.

Dr. Edith Claypole, who has done most of the laboratory work on the specimens, has by means of various

devices made a large number of cultures from several cases, and with notable results that are set forth in her notes accompanying this paper. By Gram-stain and otherwise she has been able to demonstrate in the sputum the mycelial threads and rod-segments many days before they appear in masses large enough to give the peculiar radiating appearance so characteristic of the *Streptothrix actinomyces*—indeed, in the early stage she feels able to predict that the larger masses will be found later. This is, I think, a discovery of distinct value. She suggests that any specimen of sputum containing faint blue-staining bacilli in notable numbers, which persistently refuse to grow in ordinary media and are Gram-positive, should be critically searched for the streptothrix with almost a certainty of finding it.

The appearance of the germs, both to the naked eye and magnified, has tallied with the classic description of *Streptothrix actinomyces,* except that there have been no true "clubs," and it has been substantially the same in all the patients. Several authors who have discussed this phase of the subject, notably McFarland, regard the clubbing as merely incidental and unessential in the growth of the germs. This is the correct view, and the clubs are most unusual in the human pulmonary infection,[2] for the reason that being probably a sort of by-

2. The following writers are on record as holding that the clubs are non-essential:

Bevan, A. D.: Ann. Surg., 1905, xli, 641.
Hitchins, P. S.: Brit. Med. Jour., 1905, ii, 1168.
Hodenpyl: Med. Rec., 1890, xxxviii, 653.
Levy and Klemperer: Elements of Clinical Bacteriology, 1900, p. 356.
Litton and Levy: Deutsch. med. Wchnschr., 1906, xxxii, 1772.
Lord, F. T.: THE JOURNAL A. M. A., Oct. 8, 1910, p. 1261.
Ruhrah, J.: Ann. Surg., 1899, xxx, No. 4, p. 417; No. 5, p. 605; No. 6, p. 722.
Stokes, W. R.: Am. Jour. Med. Sc., 1904, cxxviii, 861.
Werthen and Olney: Am. Jour. Med. Sc., 1904, cxxviii, 637.
Wood and Eshner: Med. Rec., 1910, lxxvii, 947.
Wynn, W. H.: Brt. Med. Jour., 1908, i, 554.

The following claim that neither granules nor clubs are essential:

Ashton and Norris: THE JOURNAL A. M. A., Sept. 9, 1905, p. 784.
Beracz, R. von: Ann. Surg., 1903, xxxvii, 336.
Caglieri, G. E.: THE JOURNAL A. M. A., Nov. 12, 1898, p. 1173.
Chiari: Ztschr. f. Heilk., 1900, ii.
Hamm: Deutsch. med. Wchnschr., 1906, xxxii, 941.
Letten and Levy: Ztschr. f. Heilk., 1900, ii.
Musser and Gwyn: Tr. Assn. Am. Physicians, 1901, xvi, 208.
Scheele and Petrusky: Deutsch. med. Wchnschr., 1897, xxiii.
Wagner, C.: Surg., Gynec. and Obst., 1910, x, 148.

product and depending on the character of the host-tissue, the lungs do not favor their growth. Neither do they grow in any of our culture media. The essential elements are the mycelial threads and their fragmentations, rods and granules, and they tend to gather in masses with certain characteristics that have given the name "actinomyces" to some of them.

The presence in most of the cases of bloody expectoration at some period of the disease, and especially the frequent bad odor, indicate true *Streptothrix actinomyces*. But, of course, some other variety of streptothrix might possibly produce all the phenomena noted in these cases, and they may represent more than one variety. That the germs are an incident and not an etiologic factor in the cases described is quite impossible. The causative relation to the disease is as certain for these germs (whatever their classification) as is that of tubercle bacilli for pulmonary tuberculosis. There may, indeed, be a close biologic relation between the streptothrix and the tubercle germs, but if such is the case it does not appear to be so clinically.

Dr. Claypole has written the following note and discussion on the specimens, and on the pathology of the disease:

In the majority of cases the sputum is characteristic and of two types; (1) glairy, mucilaginous, often quite watery; (2) purulent, more or less bloody, more or less—sometimes intensely—fetid. Both types may be found sparingly or in abundance. The second type may only have a characteristic, homogenous, pinkish color, or be deeply blood-stained; it generally has a distinctly bad odor. This odor may belong in some degree to both kinds of sputum, but especially to the purulent form. Of eight cases, not complicated with tuberculosis, three were in Class 1 and five in Class 2.

The small granules, usually the size of a very small pinhead, can be picked out with a needle and put on a slide for examination. They are quite tough and can be washed free of debris by putting them into a small dish of water and squirting them vigorously up and down a pipette. Careful examination of many specimens before and after this treat-

ment shows them to be absolutely unhurt by it; only the pus and epithelial cells clinging to the outside are removed.

Under a low magnification (Reichert objective 1 and ocular 1) the yellow color is marked; to the naked eye the fungus is greyish white. The edge is always darker, even shading into brown; toward the center it grows lighter. From this light, almost homogeneous center, the characteristic radiations arise. Higher magnification (Reichert objective 7 and ocular 1) shows the center to be a mass of pale, radiating threads, the mycelium, and at the edges a mass of threads and cocci. Both mycelium and cocci may be stained with methyl blue, the former frequently being banded light and dark in segments, sometimes granular throughout.

Culturally, the actinomyces do not grow usually on plain agar, glycerin and glucose agar, or potato (they do not seem to be more active on one than on the other of these media); if they are present, there are small whitish masses on the surface, which on removal give the characteristic appearance under the microscope. In bouillon the germs grow better.

In Case 14, T., long bacilli are recorded as found in the sputum at first and later the characteristic granules of streptothrix. In all probability these bacilli, so-called, are fragmented mycelium; ultimately the fungus appeared in masses of tangled mycelia rather than in granules, but always some material of this sort was found. In about eight months a cavity appeared at the apex and the lung involvement became more extensive, especially posteriorly.

When death occurred, the emaciation was extreme. The left lung and pericardium were normal; the right was contracted and anteriorly over the third and fourth rib cartilages, the parietal and visceral pleurae were densely adherent and the bone involvement marked, explaining the neuralgia and substernal pains complained of. When the adhesions were separated the lower part of the pleural cavity was found to contain 8 ounces of most fetid pus. For a few days before death the patient had coughed up quantities of this fetid fluid, at times almost suffocating in it, showing a bronchial communication with the cavity.

The upper lobe of the lung was mottled black and white, was almost solid in consistence, no porous structure remaining; it contained several small cavities from the size of a pea to that of a walnut. The middle lobe was dark red, spongy, with whitish spots, and anteriorly a white, honey-combed area that was adherent to the sternum for a space of some 3 inches. This was evidently the most recent involvement.

The lower lobe was contracted, reddish and somewhat porous. The diaphragmatic pleural surface was much thickened and

resembled a pyogenic membrane. The same mycelial masses were found in this fetid pus as had been observed in the sputum. When the lung was cut into, the same granules and mycelial masses were found in the larger bronchial tubes, together with the debris of pus and epithelial cells. There was no evidence of any lymphatic involvement in any of the bronchial or other glands.

The microscopic examination of the tissues demonstrated the growth of the fungus from the earliest stage to the mycelial masses. Sections were made from the consolidated apex, the middle lobe near the adherent portion, the intercostal tissue, the reddish lung near the base and a piece of the thickened inferior pleural surface of the lower lobe. Some sections were stained with hematoxylin and eosin, and others by the Gram-Weigert method.

As shown in the hematoxylin-eosin mounts, the upper lobe consisted of a large amount of fibrous material, much new granulomatous tissues but no alveoli. The bronchial tubes of varying sizes remained more or less full of sputum, and scattered among the granulomatous tissues were giant cells, not like those accompanying tuberculosis, but small, with only from four to eight nuclei. Never was there any sign of caseation; everything was dense and compact. In the other lobes there was some vesicular structure, but the alveoli were full of desquamated epithelial and pus cells.

Throughout the lung patches of new-formed granulomatous tissue, with its accompanying small giant cells, were of frequent occurrence, showing tissue response to some form of irritation. In places a fine fibrillar structure was plainly seen, often apparently in circular spaces, suggesting blood-vessels. This was of especial interest, as will be seen from the revelations made by the application of the Gram-Weigert method to the same set of sections.

In a recent series of lectures by Foulerton in the London *Lancet* the whole subject of streptothricosis is most ably discussed, and the complex morphology clearly demonstrated. The reproduction from the mycelium of rod-segments, very similar in appearance and morphologically equivalent to bacilli, as well as by spores, is an especially illuminating phase of the problem and one which gives an entirely new point of view from which to investigate all the tissues in this disease. The Gram stain shows these small particles in the newly infected areas, when other methods fail to do so.

In this case the point of most recent invasion is the area of the middle lobe adherent to the chest wall. This is the point at which the study logically begins. The tissue is more nearly normal than elsewhere, some exudation into the alveoli and some granulomatous cells are present. In one of the largest bronchioles full of pus cells and other elements of sputum, the most beautiful picture of the method of invasion is found. Rod-segments, staining blackish with Gram stain, literally swarm in one place among the pus cells. High columnar epithelial cells surround this mass of sputum. At one point their integrity is broken, and in among the cells are masses of these black rod-segments en route to the deeper tissues. Again, they are found in the intercellular connective tissue and even to the fibrous tissue surrounding the small blood-vessels. This is of especial interest in view of the fact that in older areas of infection these open spaces with walls apparently like those of vessels are found filled with mycelial threads staining the characteristic blue. The good condition, relatively speaking, of all the tissues entirely negatives the idea that this is a process of discharge into the bronchiole, rather than an invasion of it. Of course, it is a condition of self-infection but it shows how the disease extends, and also accounts for the rather slow manner of extension, that of contiguity, not by infection through the blood-stream.

The development of these rod-segments into the typical mycelial masses is the next point for demonstration. The earliest stage of the growth of the mycelium from the rod-segment could not be determined, the reason for this being indicated in the cultural experiments described later. In the sections of the reddish porous part of the middle lobe, rod-segments are also found in the interalveolar tissue, also small granules of the fungus. There are many granulomatous patches and in them are found areas of interlaced fibrils staining more or less deeply with Gram stain, also masses of

fibrillar substance likewise staining blue. Small fragments of mycelium can be found in the exudate in the larger bronchioles over this area also. There occur in the larger bronchial tubes some sections of the tufts of the fungus; these stain deep blue and are very distinct and characteristic. Small scattered fragments of mycelium are found in many parts of the sections.

In the upper lobe no air-spaces remain, fibrous and granulomatous tissue alone are found with some blood-vessels and a few bronchial tubes; in these can be seen fragments of mycelium. The response to the extreme irritation of the parasite is the formation of new tissue, and the air-cells are destroyed. Apparently, the excessive new formation of tissue is unfavorable to the fungoid growth; it disappears. The parasite departs but the function of the lung is destroyed. Further invasion of new, softer tissues presumably occurs with similar results. This total lung destruction probably accounts for the marked short-windedness of most of the patients afflicted with this disease, indicated in physical signs by the so-called extreme fibrosis.

At what point the mycelium begins to form rod-segments is at present undetermined. They may form only when conditions become unfavorable for growth in any special region, or they may be formed in small numbers at all times. The former would be the more probable, however, in view of the larger number found at the place of invasion in the most recently infected point. It is possible that the masses of mycelium, usually found in the sputum, are not capable of entering new tissues, in fact cannot cause infection; that is, that they must become rod-segments before really being dangerous to the system.

The peculiar manner in which the rod-segments surround the small blood-vessels is worthy of further study. Finding the interlaced mycelial threads apparently in blood-vessels was at first very puzzling, and only after

the earlier stage of the process[3] was discovered did it seem possible that the fungus really was in the vessels.

### SUMMARY

1. A large amount of granulomatous tissue takes the place of all air-sacs and small bronchioles in the final stage.

2. Marked absence of caseation and very little breaking down save in a pleural cavity.

The in many ways unexpected results obtained from the study of the tissues in this one case of primary streptothricosis of the lung make it most desirable that more should be critically examined to determine if the course of the pathologic changes is always the same or if noteworthy variation occurs.

### CULTURAL AND SPUTUM EXPERIMENTS

To investigate more fully the character of the infectious agent responsible for the disease in these cases, a series of cultural experiments were made from Cases 9 and 17.

The contaminations unavoidable in sputum and the very poor growth of the organism on solid media made it impossible to obtain pure cultures without a much longer series of experiments than time allowed. The ordinary streak and plate methods are not suitable, since the secondary forms, growing freely, cover the surface before the streptothrix is started. Consequently bouillon was chosen and contaminating forms, chiefly staphylococci, disregarded. The small granules found in the sputum, consisting of tufts of mycelium, were carefully picked out either with a needle or pipette, washed thoroughly in repeated changes of sterile water and then either crushed or dropped whole into the tubes which were incubated at 37.5 C. and examined daily in hanging drops and smears, the latter stained with methylen-blue by the Gram method.

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3. Pollack, Lohlein and Chiari report organisms in blood-vessels of lung and other tissues.

In the hanging drop the growth of the organism is beautifully shown; in the earliest stage (twelve hours) it apparently consists of a few spores, and from them two or three delicate threads of mycelium; both stained and hanging drop mounts show this clearly. During the second, third and fourth days the small organism grows rapidly, becoming quite a mass of threads, radiating with more or less regularity from the center of growth. By the sixth day small but distinct granules can be seen in the bouillon; these are large enough to pick up and crush on slides to make smears. On agar the growth is but feeble, never in isolated masses, owing to the presence of more rapidly growing organisms, and not recognizable to the naked eye as separate masses. In hanging drops and smears it shows fragmented mycelium and rod-segments in abundance. The little tufts in the bouillon are tangled hycelium beset with many coccus-like spores, strongly Gram-positive.

In the early stages, up to the fourth day, the mycelium proved itself to be very resistant to stains of all kinds, only a few threads becoming colored even after prolonged treatment and none if merely the usual time was allowed. Parallel observations on the hanging drops showed the fungus to be present in abundance. Finally, by the time the small tufts became visible to the naked eye, on the fourth day, the usual staining properties began to appear and by the sixth day successful operations resulted from the standard method. At no time, however, was the organism acid-fast.

The application of the Gram stain to this organism discloses many points in the structure not shown by the ordinary stains. There is a great variation in the diameter of the different threads and as marked a difference in their staining qualities. Some are fine and hair-like, others coarse and thick. Many of the heavy ones stain a deep continuous blue, others are finely granular throughout, some segmented at regular intervals, like long strings of large bacilli, again like strings of strepto-

cocci, or in separate organisms, like bacilli; the rod-segments among those that take the Gram stain in whole or part are many that show only the counter stain and even that faintly; some are large, some small; the very young and the old degenerate threads. After becoming familiar with the organism it is easy to trace the same irregularity in staining in the tissues, though here the fragmentation is not a marked phase, save where the formation of rod-segments has occurred. The resistance to stain of the young mycelium also serves to explain the notable absence in the tissues of very young forms growing from the rod-segments. It is a well-known fact that microorganisms in tissues are more difficult to stain than in pus, sputum or cultures. It may be the difficulty in hardening the tissues rapidly enough to fix the organisms. In the case under consideration it would seem to be some qualities in the organisms themselves. Only as they grow old they lose the power and again fail to color typically. The exact conditions under which the rod-segments form are as yet not determined. It is evident that by no means does all mycelium fragment into them. Much of it dies, as evidenced by fine granulation and final lack of stain.

SUMMARY

1. The fungus is found to be markedly pleomorphic, occurring in (a) the classical grain or tuft, in culture and tissue, (b) fragmentations, bacillary, or even smaller, like granules, in tissues and discharges and some culture (solid) media. Very variable in size of mycelium.

2. The very young mycelium is resistant to all stains; the old threads likewise fail to stain.

3. In cultures and tufts the mycelial masses always show large numbers of small Gram-positive organisms (spores). Fine branching mycelium in the very early stage starts from these structures (demonstrated in hanging drops and smears). They are negative to

Moeller's method for staining spores of ordinary fission fungi. They were not demonstrated in the tissues.

4. The active infectious agent in tissues is apparently the rod-segment.

To extend the study somewhat further a series of preparations was made from the sputum of many patients, tuberculous and others, as well as from Cases 9 and 17. This was to determine whether the Gram-picture was diagnostic of the disease and whether it appeared in sputum in the absence of microscopic tufts. No tuberculous sputum showed the same results. In Cases 9 and 17 particles of sputum chosen, carefully avoiding any macroscopic piece of the fungus, invariably gave rod-segments and fragmented mycelium. At one time when the pus appearance of the sputum was negative in Case 9 the rod-segments and mycelium showed abundantly by Gram stain.

Culture in bouillon always gave positive results in the absence of fungus in the sputum visible to the naked eye. By these two methods moreover, the Gram stain and bouillon culture, a case that was under observation for diagnosis was suspected and proved to be positive to culture. In a few days with severe coughing and profuse expectoration the macroscopic granules appeared, clinching the diagnosis.

If continued observations show these two methods to be absolutely trustworthy it will be possible to make an early and reliable diagnosis for this disease. The simplicity of a bouillon culture and hanging drop examination, together with some Gram-stained films, brings it within the reach of all who are near any sort of laboratory facilities.

Auditorium Building.

# EFFECTS OF HYPODERMIC INJECTION ON THE SECONDARY ANEMIA OF CHRONIC PULMONARY TUBERCULOSIS

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LOS ANGELES

For several years iron preparations have been used hypodermatically in the treatment of secondary, and arsenic in the treatment of pernicious, anemia. In 1908 Peters[1] reported favorable results after two years' use of iron citrate hypodermatically in the treatment of secondary anemia of tuberculosis, employing a number of formulas of different combinations.

Later Morse[2] reported satisfactory results even in severe cases with citrate of iron subcutaneously in the treatment of anemia in infancy. He found the rise in the percentage of hemoglobin was more rapid than that in the number of red blood-corpuscles.

Dickinson,[3] on hypodermic treatment of anemia, says where medicinal preparations fail, when the anemia cannot be relieved, and where digestion is markedly embarrassed by medication, the hypodermic use of iron must be resorted to. Each of these authors speaks of the pain caused at the site of injection.

Of the beneficial effects of arsenic preparations hypodermatically, much has been published in recent years. It is to consider chiefly the use of organic preparations of arsenic in secondary anemia that this paper is written.

1. Peters, Leroy S.: Med. Rec., Oct. 10, 1908.
2. Morse, John Lovett: THE JOURNAL A. M. A., July 10, 1909, p. 107.
3. Dickinson, G. K.: Med. Rec., Sept. 3, 1910.

Our attention was first called to this treatment one and one-half years ago by Dr. Bullock, at Silver City, who showed some results that seemed most favorable and asked one of us (Barlow) to try its effects here.

CASES

Twenty-eight patients were treated, thirteen of whom were in Stage II and fifteen in Stage III.

Many of the first twenty patients had shown little if any improvement on the regular hygienic-dietetic treatment. Some had lost in weight, some had been for a considerable time stationary in weight, and some had gained slowly, though still below their average weight in health. No early case was taken for the reason that such have, without exception, recovered under the routine treatment, or without special agents. It was desired to test the treatment on individuals for whom the routine treatment seemed insufficient. Some of the first twenty cases were looked on as hopeless (2, 8, 14 and 19), and others as capable of nothing more than improvement or arrest (1, 10, 13, 15, 16, 17, 18). In five cases, in Stage II, the prognosis was "fairly good," or "good" (3, 4, 5, 7 and 11); one, in Stage III, was a case of tuberculosis of the larynx, which had healed during tuberculin treatment and absolute rest for the voice for eight months. In this case, the weight had gone down under the higher doses of tuberculin (B.F.), although no febrile reaction was noted at any time, and the low weight was the special indication for the treatment here discussed.

In the second group of eight cases, three were in Stage III, and five were in Stage II, altogether a more favorable class of cases, although one was far advanced (25), and four (21, 24, 25, 28) were capable of nothing more than arrest or improvement of the disease. In one case, treatment was abandoned after one month because of the complaints of a neurotic patient, and because the injection was followed by such severe reaction at the site of injection, ecchymosis, swelling, tenderness, local fever,

etc. This case is not included in the number under discussion.

PREPARATIONS USED FOR INJECTIONS

Early in our experience three patients received Italian preparations, e.g., citrate of iron with strychnin, or metarsenate of iron, etc. As these individuals received the domestic preparations over a much longer period of time, we shall not complicate the report by unnecessary details but shall report on the three principal preparations used: (1) iron cacodylate, (2) sodium cacodylate, and (3) arsacetin.

1. *Cacodylate of Iron.*—This is said to be iron in combination with cacodylic acid, $(CH_3)_2AsOOH$, and therefore an organic form of iron and arsenic. "Those organic arsenic combinations in which the metallic atom is directly attached to the carbon are only feebly poisonous, but in time seem to be changed to arsenious acid in the tissues and may then cause typical poisoning." (Cushny[4]). The combination used is put up in sterile ampules of glass, each holding 1 c.c. of the solution, which is a dose of 0.03 gm., i. e., 30 mg. The solution is of a reddish color, clear and transparent, keeps well without sedimentation or deterioration. When injected beneath the skin or into a muscle, it causes a sharp stabbing pain which passes away, usually within a few minutes, but which has been seen to persist for twelve to eighteen hours. Occasionally, discoloration of the skin, as from ecchymosis, is observed for as long as ten days, either with or without continued pain and tenderness in the part. In one case we discontinued the treatment on account of the intensity of the reaction, the patient being neurotic and reluctant to continue. In nearly all cases there is some induration at the site of injection, although it usually passes away within two days and is not commonly painful.

4. Cushny's Text-Book.

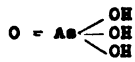
2. *Sodium Cacodylate.*—This contains sodium in combination with cacodylic acid. It is put up in the same sterile ampules as is the iron. It is a clear, colorless, watery solution, and the single dose is 1 c.c., which, in the strength used here, contains 0.05 gm., i. e., 50 mg. This solution also keeps well without clouding or depositing sediment. When injected beneath the skin or into a muscle it causes only slight discomfort or none at all, and we have seen no induration, ecchymosis or continued pain follow its use. When given twice a week, the same site for all injections may be employed if desired.

3. *Arsacetin.*—This is an acetyl derivative of atoxyl and is said to be much less toxic and much more stable than that more familiar drug. Atoxyl is $C_6H_5NHAsO_2$ and contains 37 per cent. of arsenic. Arsacetin is also put up in sterile ampules, each containing 2 c.c. of a 10 per cent. solution which is a dose of 0.2 gm., i. e., 200 mg. When sterilized in dilute solution it does not cloud and keeps better than when in more concentrated form.

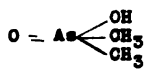
Of each drug a single dose is contained in an ampule and the preparation is sterile and ready for use. A needle 1 to 1¼ inches in length and of small caliber, with a glass syringe of the required capacity (1-2 c.c.), is boiled and after the skin is cleansed with 95 per cent. alcohol, and the solution drawn into the syringe from the broken end of the ampule, the solution is injected deep into some muscle easily reached. We have most commonly used the deltoid muscle. Injections into the gluteal muscle would cause less pain, but the deltoid is very much more readily accessible and the pain is so slight that the patients prefer the more convenient location and offer little or no objection to the discomfort which accompanies it. So far, we have seen no abscess, and with even reasonable care none should occur. Occasionally, we have injected the various drugs just under the skin, but the intramuscular administration seems preferable on account of better absorption. Two injec-

tions a week have been given as routine; more frequent administration could doubtless be employed.

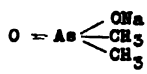
(1) Arsenic acid



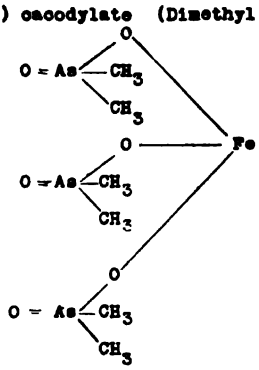
(2) Cacodylic acid (Dimethyl arsenic acid)



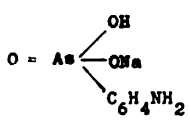
(3) Sodium cacodylate (Dimethyl sodium arsenate)



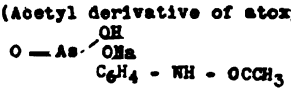
(4) Iron(ferric) cacodylate (Dimethyl ferric arsenate)



(5) Atoxyl (para-amido-phenyl-sodium arsenate)
(sodium salt of arsanilic acid



(6) Arsacetin (Acetyl derivative of atoxyl)



DEGREE OF ANEMIA BEFORE TREATMENT

In our experience, pulmonary tuberculosis does not cause a severe grade of anemia. The hemoglobin is rela-

tively low as compared with the number of red blood-cells, thus giving a color index of less than 1. In the blood-examinations made before treatment, the lowest estimation of hemoglobin by the Sahli hemometer was 54 per cent., which was accompanied by a red-count of 3,904,000, giving a color-index of 0.69. The highest hemoglobin in this series was 94 per cent., with a red count of 5,472,000, a color index of 0.87. The average hemoglobin content for the twenty-eight cases was 81 per cent., the average red count was 4,904,428, with an average color index of 0.826. Of the twenty-eight counts, sixteen were 5,000,000 or more, while only three were below 4,500,000. The rest were between 4,500,000 and 5,000,000.

In the leukocyte counts there was nothing especially noteworthy, for all being advanced cases, clinically, a slight increase in leukocytes was the rule, ten being 10,000 or more, the highest count reaching 15,400. In six cases the leukocytes were under 7,500, in one it was as low as 5,400, this being a case with very little moisture. In general, we may say that the patients with a large amount of moisture, i. e., with copious sputum and many moist râles in the lungs, showed an increase in leukocytes, the increase affecting the neutrophilic polymorphonuclear cells particularly, while the comparatively dry cases showed a normal or low leukocyte count, with the relative proportions normal, or a slight increase in the relative number of mononuclear cells present. This conforms, in a general way, with our ideas based on a much larger number of blood-examinations than we report here. For differential counting of the leukocytes we used the Ehrlich triple stain, fixing the smears by heat and counting always five hundred cells.

### EFFECTS OF THE TREATMENT ON THE BLOOD

Of the twenty-eight patients treated, there were two for whom we have no blood-count made after treatment, in one case because the patient had to be sent away as a

matter of discipline, and in the other because the patient died suddenly from acute dilatation of the right heart (?). With these exceptions, we can give the record of the blood-examination after treatment.

After treatment, the highest count was 6,170,000, having gone up from 5,216,000. The highest hemoglobin was 96 per cent. (Sahli), which, being accompanied by a count of 5,664,000, gives a color index of 0.85. The average red count in the twenty-one cases which showed improvement in the blood was 5,355,857, as compared with the previous average for the entire twenty-eight of 4,904,428, which is also an average gain, for those twenty who gained, of 542,712. On the other hand, five patients lost in the number of red cells in the blood, all of the five being patients who did badly, except one, who had 5,376,000 at the start, showing an average loss of 319,000 cells per c.mm.

The hemoglobin changes were as follows: twenty-four patients gained in hemoglobin, the average gain being 8.46 per cent., with a maximum gain of 18 per cent. (cases 14 and 25). Two lost in hemoglobin, the average loss being 2.5 per cent., with a maximum loss of 3 per cent. Of the twenty-four who gained in hemoglobin, the average hemoglobin content after treatment was 88.54 per cent. With the average count of 5,355,857, we derive the color index of 0.835, as compared with the average color index of 0.826 before treatment. Thus the type of anemia, in so far as any anemia exists, is unchanged, the increase or improvement affecting the red-cell count and the hemoglobin in practically the same degree. However, we must remember that the number of patients who showed an increase in hemoglobin was twenty-four as against twenty-one who showed an increase in the red count. The improvement in hemoglobin seems, therefore, slightly more frequent in this series than does the increase in the red count.

As to the behavior of the leukocytes under treatment, in general, those counts which had been increased appear

to be reduced toward the normal, and the lower counts seem to have been increased slightly. So many other factors affect the number of the leukocytes that we cannot include a full discussion of this feature at this time. Those patients who had shown considerable moisture and profuse expectoration also showed high leukocyte counts at first. As the moisture diminished and the sputum became less abundant, the leukocyte count seemed to diminish. This is not at all unlike the facts as they have appeared in patients not treated by special agents in our experience, and we cannot ascribe any significance to such changes as have appeared within this series, in so far as the leukocytes are concerned. As a matter of fact, of the twenty-six cases, in ten there was a diminution in the number of leukocytes after treatment, while in sixteen there was an increase. The greatest increase was 3,000 and the greatest decrease was 6,400 (Case 5). In differential counting there was nothing of special interest determined, as the relative proportions of the various types of leukocytes seemed still to be dependent on the presence or absence of secondary infection, bronchitis, etc.

We have not separated the cases of those patients who received iron from the cases of patients who had no iron, because there is little difference in the results in the two groups. If any distinction is made, we would say that the patients who had iron show a relatively greater increase in the hemoglobin content of the blood, while those who had no iron show a greater relative increase in the number of red cells present.

### WEIGHT OF PATIENTS BEFORE TREATMENT

In all patients treated, the weight before injections were begun was below that given as the average weight in previous good health, which we take as the standard and call "normal weight" for our patients. Three patients had been under treatment by the ordinary means for fourteen months and one had been under

observation but one week before injections were begun. The average residence in the sanatorium before beginning the present treatment was 18.4 weeks. One patient was within a half pound of her normal weight and several were within five pounds of normal, but others were far below, one (2) being more than thirty pounds below his normal weight.

### EFFECTS OF TREATMENT ON THE WEIGHT

Each patient was weighed once a week, Tuesday morning, and the weight recorded on the special weight chart. Many of the patients had been a long time under observation before they were given special treatment, three as long as fourteen months, two for eleven months and others for shorter periods. In the first group of twenty cases, no patient had been in the sanatorium less than one month, and only three less than two months. In the second group of eight patients placed on the treatment, one man had been under observation but one week when he was given sodium cacodylate. Of all the twenty-eight, nine had lost in weight before the injections, with an average loss of 3.61 pounds, while eighteen had gained with an average of 4.36 pounds, and the weight of one had remained stationary since admission. We have tabulated the weights as they appeared at the end of each month of treatment, for the sake of brevity.

At the end of the first month, seven had lost (average loss, 1.93 pounds), and twenty had gained (average gain, 3.31 pounds). At the end of the second month, twenty-six were still under treatment, although two were not weighed, being too ill for that. Eight had lost (average loss, 1.84 pounds), and fourteen had gained (average gain, 2.50 pounds). This comparison is not with the weight on admission, it is a comparison with the weight at the end of the first month of treatment, showing the change occurring during the second month. During the third month, twenty-one were treated; two were not weighed, four lost with an average loss of 1.18

pounds, and fourteen gained with an average gain of 2.69 pounds. In the fourth month, fifteen patients were treated; two were not weighed, five lost weight (average loss, 1.45 pounds), and eight gained (average gain, 2.06 pounds). A number were continued on treatment for a longer period, some as long as nine months, so that all are collected under one head as "at end of treatment," where a review of weight records for the twenty-six on whom we have such records show that nine lost in weight, with an average loss of 2.50 pounds, while seventeen gained in weight, with an average gain of 6.37 pounds. We emphasize that this is a good record for a class of patients all of whom are moderately or far

TABLE 1.—EFFECTS OF TREATMENT ON WEIGHT *

| | Number of Patients | Number Who Lost | Average Loss (lbs.) | Number Who Gained | Average Gain (lbs.) | No. Who Did Not Change | Number Not Weighed | Number Dropped |
|---|---|---|---|---|---|---|---|---|
| Before treatment | 28 | 9 | 3.61 | 18 | 4.36 | 1 | . | . |
| First month of treatment. | 28 | 7 | 1.93 | 20 | 3.31 | . | 1 | . |
| Second month of treatment | 26 | 8 | 1.84 | 14 | 2.50 | 2 | 2 | 2 |
| Third month of treatment. | 21 | 4 | 1.18 | 14 | 2.69 | 1 | 2 | 7 |
| Fourth month of treatment | 15 | 5 | 1.45 | 8 | 2.06 | . | 2 | 13 |
| End of treatment | 28 | 9 | 2.50 | 17 | 6.37 | . | 2 | . |

* Maximum gain for one patient under treatment, 25 pounds (Case 20); treated eight months. Maximum loss for one patient under treatment, 5.75 pounds (Case 14); treated eight weeks.

advanced (Stage II or III—Turban). In all early cases the patients gain in weight without special treatment, a statement to which there is hardly an exception in the experience of this sanatorium.

The two patients "not weighed" were both far advanced and were confined to bed for months before death and both became extremely emaciated, although we had no means of getting exact records of weight for either patient. One (Case 2) had not only pulmonary disease but also involvement of the larynx, middle ear and small gut. The other patient was a young girl (Case 8) who had a slowly progressive caseous pneumonia and tubercu-

losis of the bowel (appendix and colon) who was kept in bed for more than eight months before her death.

The greatest gain in weight occurred in a patient who received the sodium cacodylate treatment (Case 20), while the greatest loss occurred in one who received the iron. The comparison is not a fair one, however, since the last patient had an enteritis of tuberculous origin.

| | | Iron cacodylate | Sod. cacodylate | Arsacetin |
|---|---|---|---|---|
| Gained in weight | 17 | 7 | 5 | 5 |
| Lost in weight | 9 | 4 | 4 | 1 |
| Treated period. Weights record. | 26 | 11 | 9 | 6 |

EFFECTS OF TREATMENT ON THE STRENGTH, ETC.

We have no numerical system that will adequately express the results in this matter of strength. Impressions and the personal statement of patients must be cited for what they are worth. Almost without exception, the patients treated say they "feel better" and stronger while under treatment than they did before. Several have asked to be put on injections a second time, simply because they felt stronger while taking these drugs, although the condition of their blood has not demanded a second course. In no case have we noted any effect of poisoning such as is seen in arsenical treatment at times.

We do not believe there has been any direct effect on the temperature of patients from the drug injected, at least none directly attributable to the drug. One patient (Case 10) had continued for several months to show an elevation of temperature to about 99.5 F. each evening, and had suffered from a persistent diarrhea for nearly three months before he began to get sodium cacodylate. After he had received this drug for three weeks, he began to have occasional days when the temperature did not rise as before in the afternoon, and the diarrhea left him and has not returned, though that was nine months ago. In the great majority of our cases no demonstrable change has been observed, although a slight gradual

decline in the evening elevation is seen in many cases, such as ordinarily occurs in a favorable individual who has been under sanatorium treatment a few weeks. Certainly, fever is not a contra-indication to this form of therapy.

In so far as the pulse is concerned, we have seen only such changes as are to be attributed to changes in the general condition of the patient. We have seen all of the same changes occur in similar cases who have had no such injections.

The examination of the sputum of our patients has not shown us any ground to believe in the sterilizing action or bactericidal power of either arsenic or iron, or a combination of the two, in the form or dosage here employed. The number of tubercle bacilli in the sputum of our patients showed no alteration other than we could expect from our past experience with untreated cases.

In some cases the patients have claimed to have an increased appetite and improved digestion after beginning the treatment. The fact that such claims have followed the first dose or the first two doses is in favor of an influence largely or purely psychic. We can say, on the other hand, that we have seen no digestive disturbance which we could attribute to the treatment by arsenic or by iron hypodermatically. This is not true of arsenic given in the form of Fowler's solution.

Two patients were suffering from troublesome skin lesions, eczematous in nature. These promptly and thoroughly cleared up after the arsenical preparations had been used but two or three weeks. The result was but incidental to the general treatment.

### SPECIAL INDICATIONS FOR ARSENIC OR IRON

In our experience of the past year, we have come to look on certain conditions as being indications for the use of these drugs hypodermatically:

1. When the body weight is below that which has been the average for the patient in previous good health.

2. When the blood shows an anemia, especially when the hemoglobin content is low. We see no reason for believing that the iron is superior to arsenic here, at least none other than the accepted theoretical grounds.

3. When the general strength is subnormal. Here we consider that the drugs act as "alteratives."

4. When, after the usual hygienic-dietetic treatment, improvement is slow or at a standstill.

5. Following a course of tuberculin, when the weight has fallen off, as it so commonly does with the increasing doses.

6. When some psychic stimulus is needed.

7. When there is reason to suspect the presence of syphilis. Here the cacodylate of sodium is to be preferred.

### CHOICE OF PREPARATION AND DOSAGE

The choice of the drug to be used will depend on the object in view. We would state our preferences thus:

Iron cacodylate is to be preferred:

1. When the hemoglobin content of the blood is relatively low, i. e., when the color-index is very low, say below 0.8. The dose of 0.03 gm. may be given twice or three times a week, changing the site of injection each time. There is apparently more direct stimulating effect derived from the iron solution than from the others.

2. When the patient is not neurotic and will not object to the pain accompanying the administration of the solution.

Sodium cacodylate is to be preferred:

1. When there is any suspicion of syphilis. In such cases we would use 1 c.c. of the 13 per cent. solution (0.13 gm.) three times a week, or at least twice a week.

2. When a painless solution is particularly desired. In such cases we would use 1 c.c. of the 5 per cent. solution (0.05 gm.) twice a week, as being safer than the stronger solution.

3. When there is some degree of secondary anemia, but with a color-index fairly high, as above 0.8.

Arsacetin is to be preferred:

1. When it is to be combined with tuberculin treatment.

2. When sodium cacodylate is not well tolerated.

In all cases we would use 2 c.c. of a 10 per cent. solution (0.2 gm.) and give that amount twice or three times a week, or even daily if it is desired.

### CONTRA-INDICATIONS

Although we have seen no harmful effect from the use of these drugs as described, we have avoided administration of them in certain cases:

1. During hemorrhage from the lungs. We have waited at least one week after the sputum has cleared up before resuming injections.

2. During the so-called "asthmatic" attacks of the patients with a great deal of chronic bronchitis and emphysema, fearing to irritate the mucous membranes during such seizures.

3. In all cases in which there was marked albuminuria and cylindruria.

4. Where there has been marked interference with the circulation.

### COMPARISON WITH PATIENTS NOT SO TREATED

The question arises: Have we done for these patients more than we could reasonably hope to accomplish for them by the use of the unassisted form of hygienic-dietetic treatment? If we have made the recovery of the later patients (Stages II and III) more probable, more rapid and more comfortable, then the special therapy has been useful. In order to get some light on this question, we have chosen from our records an equal number of similar patients (Stage II, 13, and Stage III, 15), and have studied the condition of their blood and of their weight in the same way as that followed for the others, though reported in briefer form.

The maximum weight gained by one individual, who was not given either iron or arsenic, was 45.75 pounds

in a period of twelve months' residence in the sanatorium. The maximum loss of weight in the untreated group was 16 pounds in a period of eighteen months' residence. Both loss and gain, therefore, are in the excess of the loss and gain seen in patients under treatment by injections. Those patients who are treated seem less liable to go far beyond their previous average weight in health, and less liable to lose rapidly and extensively during the course of their illness. More detailed comparison of the separate items will be found in the following tabulated weights:

TABLE 2.—WEIGHT IN TWENTY-EIGHT PATIENTS WHO WERE NOT GIVEN IRON OR ARSENIC

| | Number of Patients | Number Who Lost* | Average Loss (lbs.) | Number Who Gained† | Average Gain (lbs.) | Number Not Changed | Number Not Weighed | Number Dropped |
|---|---|---|---|---|---|---|---|---|
| First month | 28 | 9 | 4. | 19 | 4.18 | . | . | . |
| Second month | 28 | 5 | 1.60 | 22 | 2.96 | 1 | . | . |
| Third month | 28 | 3 | 0.50 | 22 | 2.27 | 3 | . | . |
| Fourth month | 27 | 8 | 1.65 | 16 | 2.69 | 2 | 1 | 1 |
| End of residence | 28 | 10 | 7.62 | 18 | 12.87 | . | . | . |

* Average residence 10.95 months.
† Average residence 14.47 months.

THE BLOOD IN TWENTY-EIGHT PATIENTS TREATED WITHOUT IRON OR ARSENIC

For the purpose of this discussion we shall take only the first blood-examination made after admission and the last before discharge. The entire twenty-eight cases are included. The general statements as to the type of anemia are true in all essential particulars when applied to this group, as well as when applied to the group treated. Being the same class of patients, i. e., in the same clinical condition, naturally the blood is about the same. On admission the lowest count (Case 24) was 3,190,000, with a reading of hemoglobin at 60 per cent., which gives a color-index of 0.96, a little higher than usual. The highest count on admission was 5,860,000,

TABLE 3.—TWO GROUPS COMPARED AS TO WEIGHT

| | Gained | | | | Lost | | | | No. Not Weighed | | No. Dropped | | Weighed Same | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. Treated | Average (lbs.) | Number Not Treated | Average (lbs.) | No. Treated | Average (lbs.) | Number Not Treated | Average (lbs.) | Treated | Not Treated | Treated | Not Treated | Treated | Not Treated |
| First month | 20 | 3.31 | 19 | 4.18 | 7 | 1.93 | 9 | 4.0 | 1 | . | 22 | . | . | . |
| Second month | 14 | 2.50 | 22 | 2.96 | 8 | 1.84 | 5 | 1.60 | 2 | . | . | . | 2 | 1 |
| Third month | 14 | 2.69 | 22 | 2.27 | 4 | 1.18 | 3 | 0.50 | 2 | . | 7 | 1 | 1 | 3 |
| Fourth month | 8 | 2.06 | 16 | 2.69 | 5 | 1.45 | 8 | 1.65 | 2 | 1 | 13 | 1 | . | 2 |
| End of residence | 17 | 6.37 | 18 | 12.87 | 9 | 2.50 | 10 | 7.62 | 2 | . | . | . | . | . |

in which blood the hemoglobin was estimated at 75 per cent., a color-index of 0.64. The average count of the red cells for these patients on admission was 4,753,000, with an average hemoglobin content of 76.43 per cent., giving an average color-index of 0.81. On discharge the average red count was 4,641,071, with an average hemoglobin content of 79.5 per cent., giving a color-index of 0.85. Of the twenty-eight cases, fifteen showed an increase in the number of red cells, the average increase for the fifteen being 445,466; thirteen showed a decrease in red cells, the average decrease being 494,615. Comparing the counts on admission with those on discharge, for the twenty-eight we find that in spite of the fact that the number which gained is greater than the number which lost, there is a general average loss of 111,929. This is due to the fact that the individual losses were greater than the individual gains, for the maximum loss was 1,760,000, while the maximum gain was but 970,000 cells.

TABLE 4.—COMPARATIVE VIEW OF HEMOGLOBIN AND RED CELLS

| | Average of Red Cells | | Average Hemoglobin (per cent.) | |
|---|---|---|---|---|
| On admission— | | | | |
| Treated | 4,904,428 | | 81 | |
| Not treated | 4,753,000 | | 76.43 | |
| On discharge— | | | | |
| Treated | 5,346,000 | | 88.54 | |
| Not treated | 4,641,071 | | 79.5 | |
| Average gain— | | | | |
| Treated | 542,712 | (20) | 8.46 | (24) |
| Not treated | 445,466 | (16) | 11.66 | (12) |
| Average loss— | | | | |
| Treated | 319,000 | (5) | 2.5 | (2) |
| Not treated | 494,615 | (13) | 7.14 | (7) |

TABLE 5.—COMPARATIVE VIEW OF CLINICAL RESULTS

| | Treated 28 | | Untreated 28 | | Seventh Report 65 | | Sixth Report 66 | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| Apparently cured | 6 | 21.4 | 1 | 3.57 | 7 | 10.77 | 2 | 3 |
| Disease arrested | 10 | 35.7 | 5 | 17.85 | 5 | 7.69 | 8 | 12.1 |
| Improved | 6 | 21.4 | 11 | 39.28 | 26 | 40 | 28 | 42.4 |
| Progressed | 2 | 7.1 | 6 | 21.43 | 10 | 15.38 | 16 | 24.2 |
| Died | 4 | 14.3 | 5 | 17.85 | 5 | 7.69 | 5 | 7.6 |
| Not treated (ann. rep.) | . | .... | .. | ..... | 12 | 18.46 | 7 | 10.3 |

With the hemoglobin the result is somewhat different. On admission the average hemoglobin was 76.43 per cent., and on discharge, 79.5 per cent., showing an average gain for the twenty-eight of 3.07 per cent. hemoglobin. There were twelve cases showing gains, averaging 11.66 per cent., and seven cases showing a loss of hemoglobin averaging 7.14 per cent., and nine cases in which the hemoglobin content remained unchanged.

In the leukocytes the lowest count was 5,400, and the highest count was 19,900. The counts here correspond exactly with the statements made elsewhere regarding the significance of leukocytosis, and in respect to the type of cells which are actually and relatively increased in number.

On reviewing the results of these control cases, the clinical evidence in favor of the treatment is stronger and more certain than the detailed evidence obtained by the actual weights and blood-examinations. It will be noted that the number of apparent cures has been just as large as that obtained during the seventh year of the sanatorium, although that group contained 17.01 of Stage I, while the group here reported is made up entirely of Stages II and III, the number in whom the disease was arrested was also twice that (in percentage) of those found in the sixty-five cases of the seventh year. This is more than a coincidence, and is more satisfying than the voluminous details, since the future usefulness of the patient and the time of his discharge from the institution, together with almost every other practical consideration, is determined by the clinical condition rather than by any laboratory tests. Dr. Trudeau has well stated this important fact—that careful clinical observation is after all the safest guide we have in the treatment of our tuberculous patients. Dr. Knothe reports from the Hospital of Odessa, April of this year, on cases of tuberculosis treated with atoxyl, saying:

> The value of the arsenic has been ascribed in such treatment to the healing action of the arsenic on the improved blood

**condition and the nutrition of the organism. To me it appears that the arsenic has, besides this, an actual bactericidal action against the tubercle bacilli within the body. . . . The conclusions from the cases reported may be drawn as follows: Atoxyl exerts a curative action on the disease in question, an activity which, in isolated cases where there is a possibility of comparison, surpasses the activity of the ordinary cacodylate as well as tuberculin, and which not infrequently succeeds without influencing the nutrition of the body, and at times even where weight is lost. I hold to my assertion that the positive results of treatment are to be ascribed to specific bactericidal activity on the tubercle bacilli within the organism.**

Our results do not confirm Dr. Knothe's views.

Dr. Peters' paper read at Denver this month concludes that hypodermic injections of iron are practically specific in the secondary anemia of tuberculosis. He considers the iron citrate the best suited in marked anemia, the metarsenate of sodium the best as a general tonic, arsenic and strychnin together to promote metabolism, and finally says that hypodermic injections of iron should always have a place in the treatment of tuberculosis.

### CONCLUSIONS

The following conclusions seem to us justifiable, at least in so far as our experience has taught us anything:

1. The subcutaneous or intramuscular injection of sterile solutions of arsenic or iron, or of the two in organic combination, is entirely practicable in the treatment of the tuberculous in sanatoria.

2. The effects of such medication are seen chiefly in the changes in the blood and in the body weight.

3. The preparations of iron seem to affect the hemoglobin content more profoundly than it does the number of red blood-cells.

4. The preparations of sodium cacodylate and of atoxyl (arsacetin) seem to affect the number of red cells more markedly than the hemoglobin.

5. These solutions are in no sense specifics against the tubercle bacillus, but seem to exert a general tonic or alterative action within the organism.

6. The use of these preparations is entirely safe and is not attended with danger to the patient, even when continued over a period of many months.

7. Relatively larger doses are borne when given thus than are tolerated when given by the mouth.

8. The dosage is capable of exact control and the amount of the drug absorbed is known definitely.

9. The body weight is more rapidly and more certainly raised when these preparations are employed than when the unassisted hygienic-dietetic form of treatment is maintained.

10. There is no demonstrable increased liability to pulmonary hemorrhage accompanying the use of these preparations in pulmonary tuberculosis, even with advanced cases and in the presence of progressive destruction of the lung.

2329 South Figueroa Street.

## ABSTRACT OF DISCUSSION

DR. SAMUEL D. SWOPE, Deming, N. Mex.: We find in our part of the country that there is a very marked effect following the hypodermic use of these preparations of iron and arsenic. Many of the people who come to us are in a very low physical state and it is especially noteworthy that we get, as the result of this treatment, a very quick increase in their desire for food, and also in their ability to assimilate the principles thereof. So far as I know in my limited experience no temperature reaction has followed the hypodermic injections of these preparations. There is the suggestion, however, that some of these effects might be due to the hypodermic injections. I find quite a few persons, especially those from the far east, who are very timid, not wishing the injections to be given in the gluteal region; for this reason the injections are often refused. I think that the nervous disturbances may have some effect on the febrile reaction. Dr. Bullock of Silver City, N. Mex., has had quite an extensive experience with this treatment. He reports very satisfactory results and his conclusions are very convincing.

DR. W. JARVIS BARLOW, Los Angeles: Toxic effects from the use of these preparations I have not seen. The reason is, I think, that I have not pushed the arsenic at all and I have kept the patients under treatment for a long period of time. I give these injections of arsenic twice a week; the arsenic is not pushed at all in the class of patients under discussion. I

do not see the need of it. I get no rise in the temperature; any rise in the temperature can be attributed to other reasons. Dr. Swope spoke of the patients objecting to the injections being made in the gluteal region. I use the deltoid region and I have yet to find a patient who objected to the injections there. I see no objections to giving the injections in the gluteal region, except that more pain is produced there than in the deltoid region. Dr. Fulton has spoken of the use of these preparations in cases other than pulmonary tuberculosis. I repeatedly see cases that have been carefully watched and which could be compared with tuberculous cases in a similar condition. The results on the blood are not different from what can be obtained by the regular methods. The tonic effects following the injections of arsenic is considerable and are not obtained by me with the employment of other methods.

# NEW CLINICAL VALUES IN THE TREATMENT OF THE GASTRIC NEUROSES

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ST. PAUL

The nervous dyspeptic has ever been a joy to the quack, the *bête noire* of the honest surgeon and internist, and a mystery to all three. Some have treated him as an hypochondriac, others so seriously as vainly to explore his interior, and yet others have sought to enfold him in that ample but threadbare diagnostic cloak which we term neurasthenia. He has been sanguinely drugged by some, abandoned as hopeless by others, and passed from hand to hand until travelling has become a fixed habit of the well to do of his species.

Those who have read the delightful lectures of Louis Bourget will recall his deliciously satirical yet true picture of the extreme form of this ailment. We also have encountered the patient with the notebook which by its copious entries of intimate yet trivial events so well expresses the vicious introspection of the unfortunate autobiographist. We have all listlessly read the distinguished names appended to his over-growing collection of prescriptions, the headings of which may constitute a complete list of continental spas.

This extreme type which even Bourget speaks of hopelessly as *diese unheilbare Krankengruppe* is fortunately the exception, and between this and the trivial and transient varieties one finds that great group of pronounced dyspeptics who represent 70 per cent. of all cases consulting the gastrologist.

No ailment is more protean in its manifestations, and because of this fact and an entire misconception of the underlying causes, its victims have in the past too generally suffered from over treatment, mistaken treatment or absolute neglect, according to the attitude, point of view or therapeutic bias of the physician consulted.

Nervous dyspepsia manifests itself through various disturbances of the nervous mechanism of ingestion and digestion. It is essentially functional in character, concerns both secretory and motor activities, and may represent either excitation or depression of function.

Ingestion and digestion are dominated and controlled by the nervous system and a modern writer reminds us of the fact that ingestion alone demands the efficient centrifugal activity of the trigeminus, glossopharyngeus and hypoglossus, and the centripetal activity, integrity, and exact coordination of centers located in the optic thalamus, rhomboid fossa, corpora quadrigemina and anterior frontal convolutions.

The sensory and motor functions of the stomach demand not only the efficient and harmonious action of both vagus and sympathetic, but also the aid of those special senses so highly developed in the gourmand.

In the presence of malnutrition, of depressed or submerged vitality, congenital or acquired, the nervous system must suffer and complain, and proper and sufficient nutriment and efficient metabolism are indispensable to the proper correlation and transmission of those nervous impulses indispensable to normal digestion.

If then we regard the predominant type of so-called gastric neurosis as merely one expression of congenitally deficient structure and unstable function, demanding, yet always tending to depart from, a high level of nutrition, we obtain a rational explanation of its diverse relationships, bizarre manifestations and resistance to empirical treatment. We understand the successes of psychotherapists like DuBois who combine wholesome advice and proper suggestion with the upbuilding of nutrition and

we cease to marvel at the good effect of rest-cures, instituted under the inadequate but satisfying diagnosis of neurasthenia.

An understanding of fundamental conditions permits a proper differentiation of cases, rational prognosis and effective therapy.

In my opinion the gastric neuroses depend not wholly on one but on three factors which may be placed thus in the order of their importance and are for the most part seen in combination:

*1. Asthenia universalis congenita.*—By far the most frequent primary cause.

*2. Chronic starvation.*—Almost invariably associated with the asthenic cases but adequate as a primary cause.

*3. Pure psychoneurosis.*—A relatively rare factor.

Asthenia universalis congenita has been described by Prof. Bernard Stiller of Budapest in a remarkable monograph entitled "Die asthenische Konstitutionskrankheit."

In a masterly discussion he shows the general depression of vital functions and the tendency to psychoneuroses and chronic malnutrition characteristic of the condition. He asserts the almost invariable coincidence of visceral ptoses and gastric atony with slender bones, a loose costal belt, an unusually movable or floating tenth rib and a tendency to obstipation. He emphasizes the importance of the tendency to rapid loss of weight under adverse conditions, and the poor resistance to acute ailments and major surgery and thus, from old iron, welds link by link a new diagnostic and therapeutic chain.

Such individuals when at their best are usually alert and energetic, but are easily rendered psychasthenic, inclined to go beyond their strength, imaginative, emotional and impressionable, and in them we find present every element necessary to the development of a gastric neurosis under certain all too common conditions.

The second cause, chronic starvation, is intimately connected both with the asthenic habitus and to a less degree with the cases classed as psychoneuroses.

Patients suffering from digestive disturbance seek to eliminate the supposedly injurious foods or to pursue one of the faddish fasting-cures, and by this personal adverse selection aided by injurious lay suggestion, the unfortunate victim is reduced to an insufficient diet or one so exclusive as to be equally injurious.

The following brief abstract of cases will serve to illustrate these points:

CASE 1.—*Congenital asthenia, starvation, exclusive diet.*—A young married woman, ailing for eight months, bedridden, mother of four children, believed to be fatally ill with tuberculosis, presented a slight daily intermittent fever, extreme weakness and emaciation, and a marked anemia of the secondary type. The most searching examination failed to reveal any localized lesion.

Slight postinfluenzal indigestion and a foolish friend had led her to adopt an exclusive diet of meat and hot water eighteen months before.

The stigmata of congenital asthenia, including nephroptosis and gastroptosis with atony, were well marked, but prolonged rest isolation, and a mixed diet brought about a rapid gain of 40 pounds and complete and permanent recovery.

CASE 2.—*Starvation.*—A man, aged 40, complained of constant indigestion, "nervous exhaustion," progressive loss of weight (25 pounds) and insomnia. Solid food had been progressively eliminated from his diet and many meals consisted of but a few swallows of milk and buttermilk.

Rest, absolute reassurance after a complete examination, and six liberal feedings daily restored his previous weight, cured his so-called "nervous exhaustion," and permanently removed all signs of digestive disturbance.

CASE 3.—*Congenital asthenia, starvation, profound neurasthenia.*—A professional man, aged 42, and a typical neurasthenic patient of the asthenic habitus, was "desperate" and "driven to extremities," by flatulence, insomnia and chronic obstipation.

Absolutely no signs of organic disease were revealed by a most thorough examination. Under rest, reassurance, six feedings daily and a seventh at midnight if awake, without special limitation as to foods, his recovery was prompt and permanent, his weight increasing 35 pounds.

CASE 4.—*Congenital asthenia, self-starvation, simulated gastric ulcer, hysteria (anorexia nervosa).*—A young girl was admitted, apparently *in extremis* from repeated gastric hemor-

rhages, and extreme gastric intolerance. She had retained neither food nor water for the preceding seventy-two hours. Emaciation was excessive, physical weakness extreme, and the asthenic habitus typically shown. There was the usual movable kidney, a marked gastroptosis, and flabby abdominal muscles.

Examination failed to confirm the diagnosis of gastric ulcer. The girl had first fasted because of postinfluenzal indigestion, had become weak, anemic, and hysterical. had been repeatedly examined by various physicians and had heard and read much of gastric ulcer.

Her hemorrhages were spurious. No one had ever been present when blood was vomited and the stools were blood-free. No localized tenderness existed, yet pain, both spontaneous and induced by pressure, could be developed any and everywhere by suggestion.

Food or water was *instantly* returned and throughout her illness her vomiting bore no definite time relation to the digestive process. Reassurance, rest, isolation and suggestion, reinforced at the onset by the threat of gavage, enabled us to give six nutritious feedings daily after the first forty-eight hours. The girl gained for the first thirty days over a pound a day and has remained symptomless for five years.

CASE 5.—"*Malade imaginaire.*"—A stout, ruddy policeman, a peripatetic hypochondriac, accustomed to starve and gorge himself alternately, presented symptoms of gastric neurosis. His stomach was normal in size, position and secretions. The general examination was absolutely negative.

He was refused treatment with the emphatic assurance that no excuse for it existed. Leaving in anger, he next visited a notorious *x*-ray quack, received one *x*-ray exposure and a positive assurance that it had cured him, paid a fee of $100, and was healed.

Such cases could be indefinitely multiplied and would include the simple achylias, many instances in which a diagnosis of tuberculosis, gastric or duodenal ulcer, gallstones, appendicitis and even cancer had been made, but these suffice to show the effect of constitutional weakness, starvation and pure imagination in producing this ailment.

### TREATMENT

Cases of misdirected imagination need suggestion in its strongest form and little more, as is illustrated by Case 5, but the more common types demand and merit

careful consideration for their disease is not imaginary and their suffering is real and at times extreme.

Treatment should properly commence in childhood, but this phase cannot receive adequate consideration within the limits of this paper.

Under proper conditions even the severest types in the adult may be entirely relieved, but these demand an expenditure of considerable time and money on the part of the patient, and skill and tact on the part of the physician and nurse.

Treatment of the ordinary case in the adult must be based on the fundamental proposition that the patient is suffering from impaired nutrition which affects practically every organ and function of the body, and from mechanical displacements of the abdominal viscera which under such conditions assume a serious aspect, though usually symptomless when the nutrition is improved.

One seeks, therefore, to obtain for them such rest and improved nutrition as can usually be had only in a hospital and with the services of a special nurse, and in most cases a persistent psychotherapy must be maintained because of the accompanying psychasthenia.

Every attempt at cure must be initiated by a thorough examination of the entire body and especially of the stomach, and a positive and emphatic statement as to the negative or trivial findings obtained.

In the milder cases the patients, and especially such as lack the asthenic basis, may be treated as office patients or in the hospital under ward nurses, but many failures or only temporary cures must be anticipated under such conditions.

The most difficult problem is presented by the poor asthenic who cannot follow the ideal treatment. Some may be greatly benefited by proper instructions as to diet and rest, a simple explanation of the nature of their trouble and the simple procedures indicated.

The *x*-ray examination readily demonstrates the fact that gastric atony and the vertical fish-hook stomach

accompany nearly all of the gastric neuroses, and that in active cases emptying of the abnormally placed viscus is delayed from one or both of two causes — first, atony; second, spasm of the pylorus associated with hyperacidity of the gastric secretions. The pain associated with the latter is frequently confounded with that of appendicitis.

Using the pain onset as the gauge, a patient may obtain marked relief by taking a recumbent position on the right side or assuming the knee-chest position for several minutes at short intervals following a meal. Peristalsis may be further assisted by massage or by having the patient clasp the left knee and make strong intermittent pressure of the thigh against the abdomen while lying halfway between the prone and the lateral position.

Helpful suggestion, abundant nourishment taken in small quantities and at short intervals, attention to any existing anemia, and the mechanical aid afforded by the before-mentioned procedures accomplish wonders in many patients.

Stiller's work has placed the whole subject on a new foundation and in the light of our present knowledge it becomes ludicrous to treat gastric atony as a local disease or to attempt to correct secretory excesses, perversions or deficiencies by drugs and diet alone.

Furthermore, the physician is at last in a position to appreciate the *raison d'être* of the wonderfully kaleidoscopic pain picture possible in the gastric neuroses and to understand why so many of its victims bear the scars of futile operations.

Time will not permit an extended discussion and I trust that my paper will be regarded only as an attempt to call attention to the basic features of an important and distressingly common ailment offering every opportunity for successful treatment in the light of a rational etiology.

In closing I shall summarize as follows:

1. The gastric neuroses whether motor or secretory depend almost wholly on an underlying asthenia.

2. This asthenia may be acquired or temporary, may be due to self-starvation or other debilitating causes, but almost always represents a chronic congenital insufficiency of body structure and function, producing a peculiar nutritional instability.

3. So-called passive neurasthenia or psychasthenia is most frequently seen in individuals of the asthenic habitus and is but a part of the clinical picture though a genuine and troublesome complication.

4. Gastroptosis produces symptoms only in the presence of atony or marked secretory changes and does not justify primary operative procedure.

5. The same statement as to the unwisdom of operative interference applies to other displacements such as movable kidney and certain uterine malpositions.

6. Certain cases occur in which no structural abnormality exists. Of these some are due to self starvation, others occur in the robust individual who represents the *malade imaginaire.*

7. Under proper conditions the gastric neurosis of the common type justifies hopeful prognosis.

8. Pain manifestations are so variable as to site, severity, character and persistence as to lead frequently to erroneous diagnosis and futile operative interference but rational non-surgical treatment affords relief in the greater number of cases.

9. Cases of the chronic congenital type bear surgery badly and usually obtain from it either definite harm or but slight and transient improvement.

10. Simple procedures may give great relief to mild cases and to those patients whose means will not permit the institution of the proper treatment but under the latter conditions failures are frequent.

11. All severe or persistent cases demand isolation, rest and hypernutrition, combined with helpful suggestion and the minimal use of drugs.

Finally, in our modern treatment of the dominant asthenic type of gastric neurosis we are successfully attacking the most common cause of chronic invalidism.

150 Lowry Arcade.

## ABSTRACT OF DISCUSSION

DR. WALTER B. CANNON, Boston: It has long been known that the most efficient stimulus for the stomach and intestine is the mechanical stretching to which they are subjected; when we consider any mechanical stretching it means, of course, that there must be something to be stretched. This is a matter that should be kept clearly in mind. To illustrate what I mean, we may regard the effects of stretching on a rubber band. If an old rubber band is pulled out, and remains out, it is not stretched; if, on the other hand, a fresh rubber band is pulled out, and it goes back again, such a band has been stretched. The condition of the alimentary canal is somewhat analogous to the condition of the rubber band. Under certain conditions the alimentary canal is incapable of being stretched; then the introduction of materials into it does not bring about activity. This has been noticed by numerous observers. If the stomach, for instance, has been in a relaxed condition for a long time, the introduction of material will not produce peristalsis. The same thing is true of the large intestine, if it is in a similar condition of relaxation, which has continued for any length of time, the introduction of food into the organ will not result in antiperistaltic waves.

These are matters which relate to the influences of the central nervous system on the alimentary canal, and especially the influences coming through the vagus nerves; the gastro-intestinal tract to the ileocolic valve receives its "motor" impulses entirely through the vagi. If these nerves are severed, the alimentary canal for days will have only a slight activity. There is, therefore, a tonic state dependent on the connection between the alimentary canal and the central nervous system. I should like to emphasize again the point brought out by Dr. Greene with regard to the atonic condition of the alimentary canal, that it is not merely a local condition but one which results from the bodily state of the whole individual. This, I believe, is a very important point and well worthy of consideration.

We have evidence to show that a tonic state of the stomach and intestines is produced when the animal takes food. I have severed the vagus nerves before the animal was given food and, as a result I have seen the food in the stomach remain there for hours. If the vagi are severed after the animal has been given food, however, digestion will go on quite undisturbed. This indicates a discharge of tonic impulses along the vagus nerves during the time the food is taken.

There are further to be considered the emotional influences, such as fear and worry, which, acting through the splanchnic nerves, cause a lessening or abolition of tonus. These influences may stop not only motor but also secretory functions. I have brought these matters before the Section because I wished to corroborate from my laboratory studies the point which Dr.

Greene has so strongly brought before you, that the activities of the gastro-intestinal tract are intimately related to the entire bodily state of the individual.

DR. FRANK BILLINGS, Chicago: I am entirely in accord with what Dr. Greene has stated in his paper. What Dr. Cannon has said agrees with what all of us have met in our clinical observations. I wish to discuss the question of surgical interference in this class of cases. The medical management, of course, must vary with every individual and with every type of patient suffering from a gastric neurosis. I think that the surgeon with widest experience has now learned that he should not interfere with these patients surgically. All over this country, I am sorry to say, there are many men who have not learned this. We continually find patients, especially in the large centers, who have been treated by surgeons and who have, of course, expected to be bettered by the treatment; they have, however, become worse. Many of them have become very miserable, and this has brought discredit on the proper management of these cases. It is to be understood that there may be a surgical side of the question in these cases sometimes. There may exist a focus of infection, for instance, which will have an influence on the nervous system and produce disturbances of the gastro-intestinal tract. These are the cases in which surgery should interfere. Sometimes there may be trouble caused by an appendicitis, by disease of the gall-bladder, or by gastric ulcer; again there may be a cystic degeneration of the ovary which causes trouble. These are the cases to which the surgeon is invited. These patients should not be interfered with surgically unless there are distinct indications.

DR. SEALE HARRIS, Mobile, Ala.: I agree with what Dr. Billings has said in regard to the surgical interference in cases of gastric neurosis. I have seen many mistakes made by surgeons in operating on these patients, and I am sure it would have been well if the paper just read could have been read before the Section on Surgery as well as before the Section on Practice of Medicine. There appears to be a tendency on the part of surgeons to operate on all patients with chronic indigestion. I recently was surprised to hear a distinguished surgeon state that if a patient suffering from indigestion did not respond to treatment in a given time, the gall-bladder should be drained or the appendix removed. Surgeons are frequently doing both operations on these unfortunate sufferers. The stomach, a few years ago, was the organ most frequently attacked by surgeons. To illustrate this phase of the question I wish to relate an instance. The patient was a woman who came to me two years ago; she had been advised by a surgeon that she had an ulcer of the stomach and that her only relief was in the operation of gastro-enterostomy. She had lost weight, she was very nervous, she had much pain, she had hyperacidity and many other symptoms of gastric ulcer. This

was a case that should have been carefully studied. After a thorough examination I was convinced that she had no gastric ulcer and that a gastro-enterostomy would probably have increased her symptoms; the operation, too, might have resulted in her death because of the low state of her nutrition. I advised the "rest cure" and employed psychotherapeutic measures with her. All the symptoms subsided in two months, without operation, and she gained 30 pounds. Many of you present, no doubt, have had similar cases.

One should make a careful and accurate examination of these patients. Indeed there is no class of cases in which the physician should be more careful in his history taking than in these patients. In getting the anamnesis it is very important not only to get a complete history of the symptoms complained of, but also of emotional disturbances to which they have been subjected, which might bring on gastric symptoms. At least 80 and, perhaps, 90 per cent. of the patients whom I have treated for digestive troubles are instances of gastric neuroses. These neuroses not only occur in women, but in business and professional men who have been overworked. When a patient comes for an examination with symptoms such as have been described, one should inquire if such a patient has been overworked. Has he had too long hours of work? Has he the worry habit? These are the things that give trouble in so many cases. The business man may have many difficulties to encounter of a financial nature; if so, he may be a sufferer from digestive disturbances. It may be the wrong husband, or wrong wife, or perhaps the proverbial mother-in-law, that is the cause of gastric symptoms in a person of neurotic temperament; if so, the readjustment of marital relations sometimes cures the patient. With regard to the treatment of the gastric neuroses in overworked business or professional men, it is apparent that their mode of life should be changed. They should work fewer hours each day, and have regular hours for rest and recreation. Eight to ten hours in bed at night and an hour's rest after the noon meal will sometimes work wonders in such cases. Such patients should also take increased nourishment and plenty of pure water between meals. This modified rest and forced feeding plan gives most excellent results.

DR. CHARLES L. GREENE, St. Paul, Minn.: I was glad to hear something regarding the work that Dr. Cannon has carried on in the laboratory in Boston; the work that he has brought before us is certainly very valuable and we are all glad to learn of it. With regard to surgery in relation to the disease under discussion, I brought this before you in my paper. One of the last patients whom I saw before leaving home was plainly a case of gastric neurosis with the neurasthenic habit very well marked. As Dr. Billings has stated, there is too much operating on these patients. As the result of treatment instituted, I have had a great improvement in

these cases during the past few years. It may be interesting to report that, on my way here, I was asked by one of our leading surgeons if he could not read the paper which I was to present before this Section. When he had finished reading it he offered only one criticism—that the surgeons had not been hit hard enough. There is no question about the value of Stiller's work in this class of cases. Any of you who have the opportunity of reading his work should do so. The only papers in English that I am aware of which deal with this subject are two in number. One was published some years ago in the *Cleveland Medical Journal* and the other appeared in the *New York Medical Journal* six or more weeks prior to this meeting. After reading Stiller's paper, as well as others that have appeared on this subject, one will have a far better idea of the stigmata of the condition which has been designated as "chronic congenital asthenia." I think it is important that the general physicians of this country should understand that this class of cases, a class of patients called "chronic invalids," was designated under the wrong term; the term employed was in fact a misnomer.

# A STUDY OF FEVER IN TUBERCULOSIS WITH REFERENCE TO ITS CAUSATION AND TREATMENT

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The fever which accompanies tuberculosis is a symptom poorly understood and unsatisfactorily treated. In recent years the opinion of the profession as to the chief factors in its causation has undergone several changes; and yet the most generally accepted theory at the present time is still unsatisfactory and leaves much to be explained. Since there can be no exactness in its therapy until we have formed some definite idea of its cause or causes, the importance of more study along this line is self-evident.

It must be obvious to anyone who has an opportunity to study patients suffering from advanced tuberculosis and who uses his powers of observation, that the cause of the chronic fever in tuberculosis and the factors which produce the irregularities in its course are numerous and complex. There has been an endeavor to make this subject entirely too simple and the result has been increased confusion.

The finding of bacteria of various kinds in the sputum of tuberculous patients, especially the pus-producers, has given grounds for the belief that tuberculosis, when it reaches the open stage, is a different process from that of early tuberculosis; and that the principal factors in the production of the symptoms in the later stages are the associated bacteria.

Koch[1] made the declaration that a daily temperature curve above 100.4 in a case of pulmonary tuberculosis

1. Koch: Deutsch. med. Wchnschr., April 1, 1897, p. 201.

is due to septic microorganisms and consequently unsuited to treatment with TR. This mixed infection theory was accepted by the profession generally. It called forth many such statements as these: "The tuberculous process is a dry process. If the tubercle breaks down it is because of mixed infection." "Cure

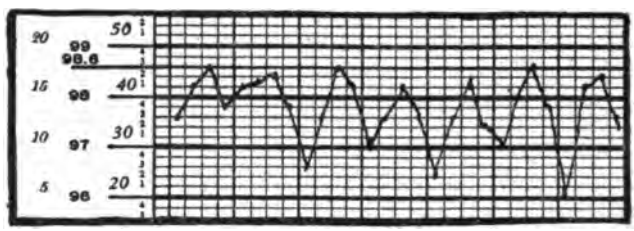


Chart 1

**Chart 1.—Fever curve of chronic fibroid tuberculosis.**

the mixed infection and the tuberculosis will cure itself." "Any temperature above 100.4 is due to mixed infection." Such statements as these were believed in spite of the fact that the débris formed in cold abscesses is moist and yet free from pus microorganisms; and in

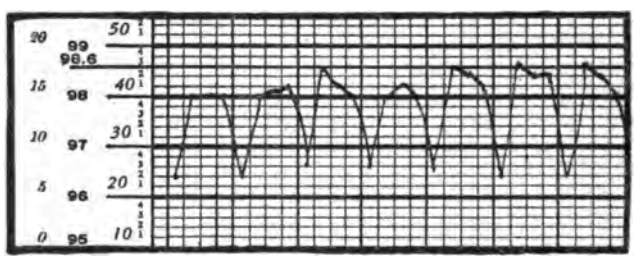


Chart 2

**Chart 2.—Fever curve of quiescent tuberculosis, ulcerative type.**

spite of the fact that patients with acute miliary tuberculosis have high temperature curves before the tubercles have reached the age of softening. See Chart 7.

In order to understand the cause of these fevers, we must take a broader view and look at the question from

many standpoints. I believe that the primary causes are at least three in number: the tubercle bacillus and its toxins; associated bacteria and their toxins; and enzymes and the products resulting from their action upon the body cells. This last cause is generally disregarded in discussions on this subject; and, yet, I

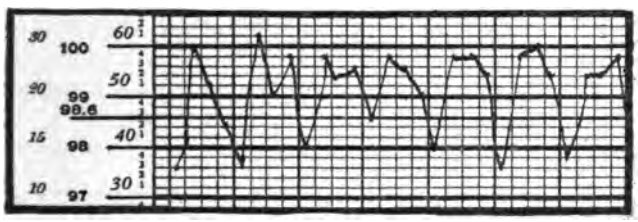


Chart 3

**Chart 3.—Fever curve showing activity in tuberculosis of chronic ulcerative type.**

believe it is a factor of great importance in all cases of advanced tuberculosis of the ulcerative type. I cannot help thinking that one of the greatest dangers to the tuberculous patient arises from the absorption of the products resulting from enzyme action.

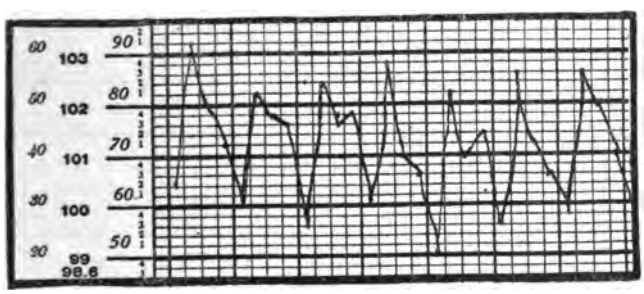


Chart 4

**Chart 4.—Fever curve of caseating pneumonic type.**

Our knowledge of the action of enzymes is as yet comparatively meagre. The writings of Hahn,[2] Ascoli

2. Hahn: Berl. klin. Wchnschr., 1897, p. 499.

and Bezzola,[3] F. Müller,[4] K. Meyer[5] and Opie[6] are very suggestive and show the value of careful study along this line.

Two factors, the tubercle bacillus and the products of autolysis, are present in all cases of advanced tuberculosis. These factors are present in varying degrees which depend somewhat on the activity of the process. I do not believe that associated bacteria are an important etiological factor in the production of all fevers which rise beyond moderate elevations in advanced tuberculosis, although they are unquestionably so in some.

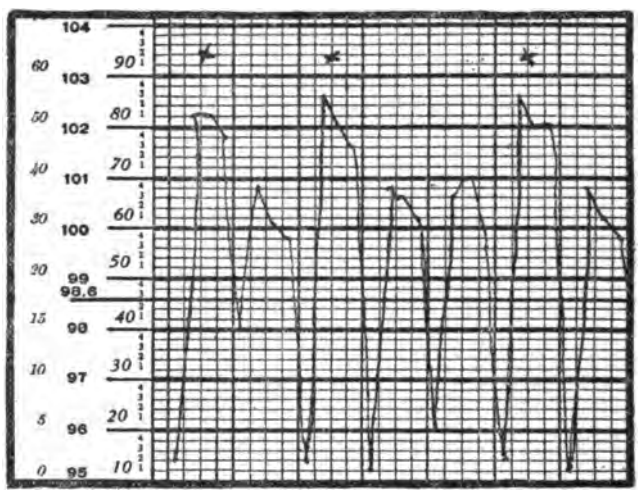


Chart 5

**Chart 5.—Fever curve of mixed infection, also showing the effect of baths in raising temperature. Crosses indicate days baths were given.**

We are wont to look on tuberculosis of the fibroid form as being due to a type of bacillus of low virulence, believing that the greater the amount of toxins or the more virulent the bacilli, the greater the tendency to

3. Ascoli and Bezzola: Berl. klin. Wchnschr., 1903, p. 391.
4. Müller, F.: Verhandl. d. 20 Cong. f. Inn. Med., 1902, p. 192.
5. Meyer, K.: Berl. klin. Wchnschr., 1909, p. 1890.
6. Opie: Report of Sixth Int. Congress on Tuberculosis, Washington, 1908, p. 255; Jour. Exper. Med., 1911, xiii, No. 1, p. 162.

tissue destruction. This is a favorable form from the standpoint of cure. I doubt not that the comparatively small amount of autolysis present is also a very important factor in rendering this a favorable form of the disease.

The ulcerative processes, on the other hand, are more serious. We assume that the tubercle toxins are a greater factor in them than they are in the fibroid form. We also must recognize that these forms present a greater amount of autolysis. Where the tubercle bacilli are supplemented by associated bacteria, we have the severest form of the disease; for here we have both the effects of the various bacteria and their toxins and an increased autolysis.

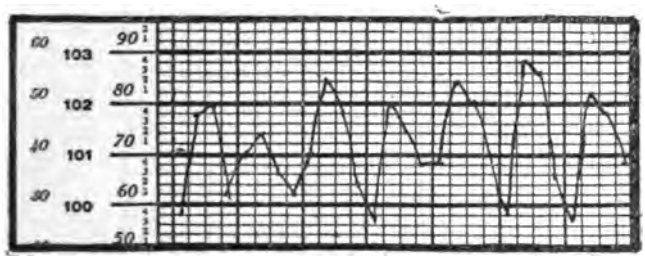


**Chart 6.—Fever curve of acute miliary tuberculosis engrafted on a chronic process.**

We have attempted with a degree of success to classify these fevers and associate certain types of temperature with certain pathologic conditions. The continuously subnormal temperature we associate with both chronic fibroid tuberculosis and chronic tuberculosis of the ulcerative type during the stage of quiescence. (See Charts 1 and 2.) Doubtless in patients suffering from these types there is a minimum amount of tubercle toxins and products of autolysis entering the blood-stream; consequently there is little or no rise in temperature. Now, if the disease becomes active, however, and the tissues begin to soften, the entire range of temperature assumes a higher level as shown in Chart 3. The morn-

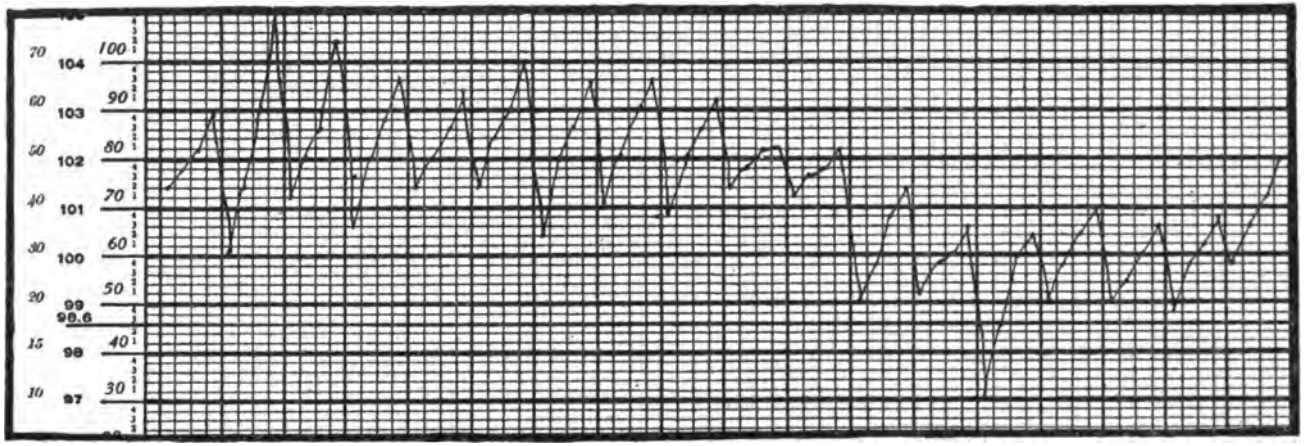


Chart 7.—Acute miliary tuberculosis, with fatal issue in about three weeks.

ing temperature rises as well as that of the afternoon. I do not doubt that the tubercle toxins are a factor in producing this increase of temperature, but I am inclined to believe that the action of enzymes may be even a more important factor; for as Opie[6] says: "Injury to tissue is due primarily to the action of the tubercle bacillus, but the occurrence of caseation is perhaps distinctly referable to autolysis." The same conditions are present in what is termed caseous tuberculosis, as shown in Chart 4. Here we must consider that practically the same phenomena are occurring as in the process which is slightly active, shown in Chart 3, but that the area of involvement is much greater; conse-

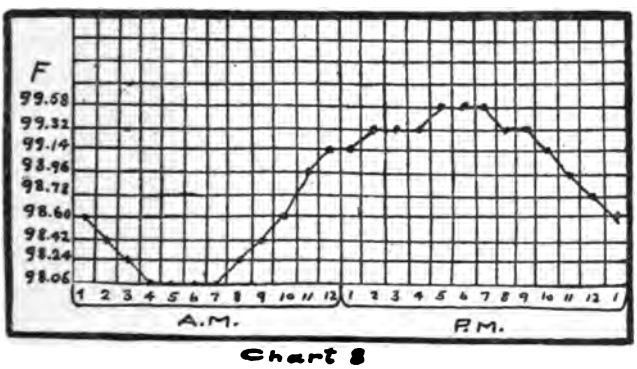


Chart 8.—Showing daily course of rectal temperature under normal conditions (after Jürgensen).

quently the temperature is higher and the symptoms on the part of the patient are more pronounced. In temperatures which are supposed to show the effect of associated bacteria, the so-called "mixed infections," we note particularly the wide daily range, starting very low in the morning and rising to a very high point in the afternoon, as in Chart 5. Here, also, autolysis must be an important factor. That we can have a continuously high fever in tuberculosis without caseation is well known. Chart 6 is the chart of a patient suffering from an acute miliary tuberculosis which was engrafted on a

chronic process, and Chart 7 an acute miliary process of sudden onset, the patient dying in three weeks' time.

A glance at the accompanying charts, bearing in mind the associated pathology, shows clearly that the greater the necrosis, that is, the greater the enzyme action, the higher the fever. Study of the clinical aspects of tuberculosis associates not only the rise of temperature, but also many of the most distressing symptoms and complications with the necrosis. How much these are due to

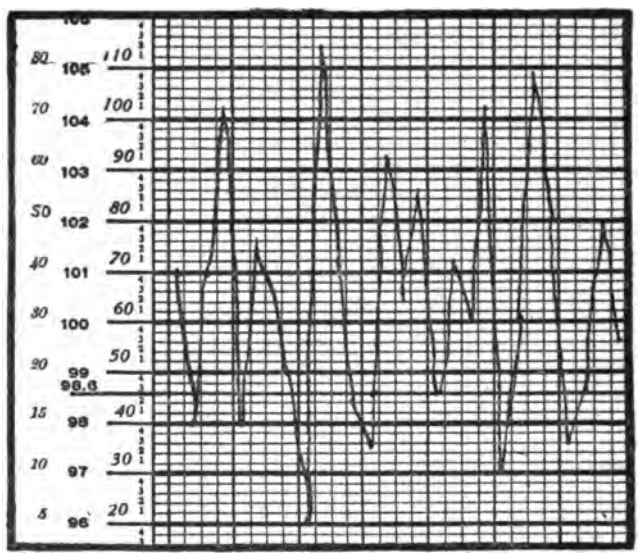


Chart 9.—Fever curve showing rapid disintegration of lung tissue, absorption of large quantities of toxins, body cells still able to react.

bacterial toxins and how much to enzymes and the products of their action remains to be determined.

In our discussion of the cause of fever we are forced to acknowledge that we are unable to explain exactly how bacteria and their toxins and the enzymes and the products resulting from their action produce fever; but there are such wide gaps in our understanding of its pathology which remain to be filled in by further study

that we are lost in a maze of uncertainty. Krehl[7] considers that the cause of fever "lies in the mechanism which regulates heat loss," and expresses the belief that "the heat in fever is produced in such a manner that it does not furnish the normal stimulus to the mechanism that increases heat loss." Roger[8] expresses the opinion that "fever is a morbid state resulting from the exaggeration of the chemical processes concerned in the production of animal heat." He looks on the rise in temperature as being due to the reaction of the organism against bacteria, their products, and other substances among which we would place enzymes and the products of their action; and, contrary to Krehl, he says:

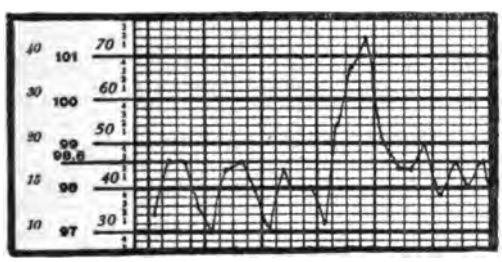


Chart 10.—Fever curve showing effect of overexertion in a chronic inactive case. Prompt return to normal.

Thus fever is due to increased chemical activity, whether or not there be a comitant departure from the normal evolution of matter. Dissipation of heat in fever is more marked than under normal conditions, but excess in the production of heat is still more marked, hence the relative retention of heat and rise of temperature.

If we assume that the normal rectal variation of daily temperature for the healthy adult is about 1.4 F., as shown in the accompanying Chart 8, after Jürgensen, and compare this with the various charts of tuberculous patients shown above, we note that when inflammation is present, the temperature as a whole rises, the variation remaining about the same for the most part except

7. Krehl: Pathologische Physiologie, 1906, p. 899
8. Roger: Infectious Diseases, trans. by Gabriel, Lea & Co., 1903, p. 333.

in a certain type of cases, notably those which we have been wont to designate as "mixed infection." The height of the curve seems to depend on the amount of chemical changes present and the powers of the organism to react. In the so-called "mixed infection" curves, there are two tendencies present. Careful study of toxins shows that their tendency is to lower temperature in large doses, while the tendency of the body cells is to react with an increase of temperature. In those cases which we are wont to designate as "mixed infection," the amount of toxic products set free seems to be very large; consequently if the patient's powers of reaction are still good, the daily range of temperature is much increased. We note the same wide range of temperature during the last days of life in cases in which we find post mortem, evidence of a recent wide-spread destruction of lung tissue. I believe we are justified in attributing it largely to absorption of the products resulting from enzyme action. While under ordinary circumstances in quiescent and slightly active tuberculosis the normal daily variation of 1.4 F. is fairly well maintained, in these conditions there is a wide departure. From the excessively large dose of toxins the temperature is markedly depressed, reaching at times several degrees below normal. If the patient's powers of reaction are good this depression is followed by a high curve. In Chart 9 it will be noted that this range in one day amounted to more than nine degrees. As the patient's power of reaction wanes, the temperature fails to reach the high points. It falls because of the toxic action and the inability of the body cells to react.

While we look on the three factors discussed above as being the primary causes of the elevations in the general temperature curves in tuberculosis, there are many factors which contribute to the variations found in these curves, some of which are subjective and others objective. Physical exertion is one of the most common causes of elevation in the temperature curve, Chart 10.

In Chart 11 the effect of an overexertion may be seen in a patient who was recovering from a chronic temperature. The effect of this overexertion was never overcome. Mental perturbation is also frequently followed by variations in the temperature curve. Thought, reading, excitement, worry, joy, disappointment and fear all have their effect. The effect of worry is well shown in Chart 12. This patient was disturbed over the illness of her mother and her temperature assumed a higher plane until the mother was better. The effect of a large meal is often seen. Intercurrent complications, such as constipation, indigestion, colds, pleurisy, toothache, as well as the more serious ones, such as pneumonia, pneumothorax, and emphysema, all affect the regular curve.

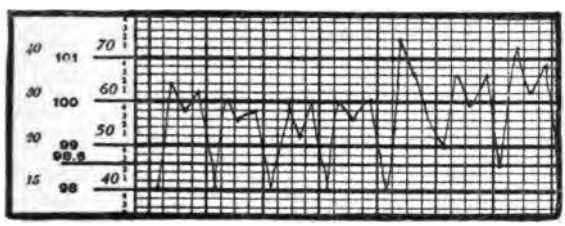


Chart 11

Chart 11.—Fever curve showing effect of overexertion in a chronic active case. Failure to return to normal.

The effect of indigestion and constipation are often shown in a rise of temperature. Chart 13 shows an acute inflammation in a tuberculous process in the lung with probable expulsion of the contents of a softened tuberculous mass. The rise was accompanied by increased cough and expectoration.

Aside from these influences within the patient, there are some without which affect the curve materially. It must be remembered that one cause of fever is lack of dissipation of heat. Therefore, it can readily be seen how thermometric and barometric changes affect the loss of body heat and consequently the temperature curve. From Chart 14 the effect of thermometric change is very plain. The low temperature on cold mornings has

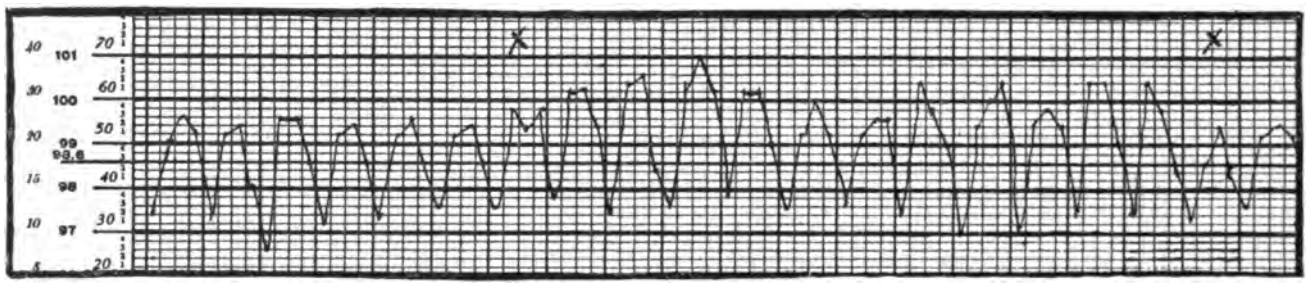


Chart 12

Chart 12.—Fever curve showing the effect of worry in patient suffering from chronic active tuberculosis. On the day marked by first star patient received word that her mother had cancer; the second star shows results of news that the diagnosis was incorrect —prompt drop in fever.

long been recognized. Another fact observed is that often a very annoying variation in temperature is produced by baths, the regular cleansing bath being followed in some patients regularly by a rise in temperature no matter how carefully the bath is given, as shown in Chart 5.

It will now be readily understood that there are so many influences which affect the temperature in the tuberculous patient that we are at times completely lost in our attempt to assign the proper cause for variations which occur. As a result of this confusion, the physician is at a loss to know the correct interpretation and the proper treatment to employ.

There has been too much of a tendency to deal in generalities in discussing the fever in tuberculosis, and the factors which produce it. It is commonly believed that every temperature above 100.4 is due to mixed infection. It is likewise believed that every patient who is having a high temperature is saturated with tuberculin which is circulating through his tissues. Nearly every rise in temperature which causes a temporary rise in the general curve is interpreted by many observers to mean an auto-inoculation of tuberculin. A moment's consideration of the underlying pathology and the conditions and influences surrounding the individual patient, however, will readily demonstrate that such general statements have no place in dealing with this disease. It is important to grasp these facts, for they have their bearing on the treatment of tuberculous fevers. At best, it will be seen that treatment of these conditions is a very complex proposition. It is especially necessary to interpret carefully the temperature curve when tuberculin is employed therapeutically.

Many of the contributing causes of fever discussed above can be avoided, while some, such as those depending on thermometric and barometric conditions, must be endured. Overexertion can be avoided by a little care. The effect of mental activity can, as a rule, be overcome.

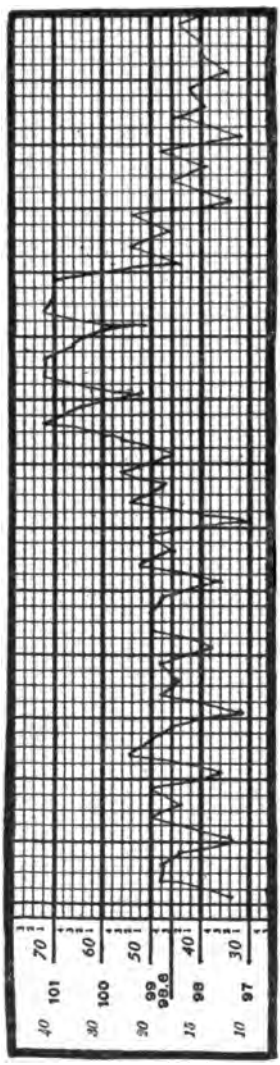


Chart 13.—Fever curve showing acute inflammation with expulsion of tuberculous material in a chronic inactive process.

Reading, thinking and excitement are largely within the power of the patient to control, while worry and disappointment can usually be avoided to a large extent if the patient and physician are in thorough sympathy with each other and are cooperating as they should. Most of the complications which arise cannot be relieved at once. Some cannot be relieved at all. Some must run a regular course; but close personal medical supervision favors accuracy of diagnosis and affords rapid relief from many of them.

The relief of the fundamental causes of fever as described above is a very difficult matter and one which will often tax the patience of the physician and patient unless both are blessed with an unusual amount of optimism.

There are certain established therapeutic principles which may be followed no matter what the cause of the fever may be; nevertheless, there are certain fundamental facts which have been continuously overlooked that must be understood if we are going to attack this condition with any degree of intelligence.

Carefully regulated hygienic living in the open air with rest for both the body and mind, food, selected according to the patient's digestive capacity, and various hydrotherapeutic measures may be advantageously employed in all cases. These measures act by improving the general nutrition of the patient so that he may withstand the effects of fever better, also by lessening some factors which increase heat production, and by bringing about conditions which favor heat loss. None of these measures has any direct effect on the bacteria and their toxins and the enzymes and the products resulting from their action which we have mentioned above as the primary causes of the fever. The primary causes must be combated by specific measures. We know that specific antibodies are formed within the body, which bring about the natural healing of specific infections. This has led to the specific treatment of many of the infectious diseases whose causative germ has been discovered.

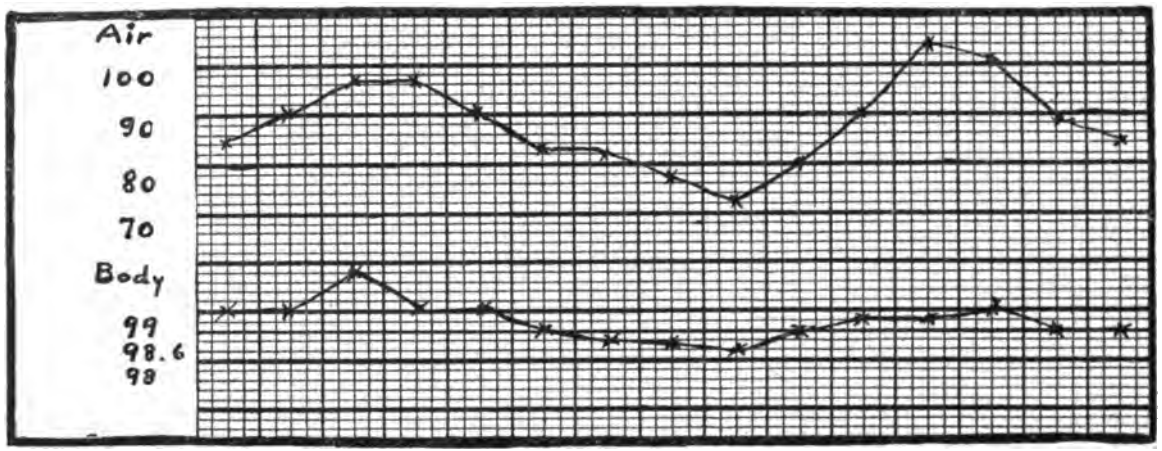


Chart 14

Chart 14.—Fever curve showing the influence of the atmospheric temperature on the body temperature. Lower curve, body temperature; upper curve, air temperature.

Tuberculin has partly won for itself, through probably the most severe trial to which a remedy has ever been subjected, the right to be considered as a specific against tuberculosis. Vaccines made from dead culture of various bacteria which we find associated with tuberculosis have proved to have specific action against pathologic conditions which are produced by their own strain. In spite of these specifics against the bacteria there are many foci which we cannot heal, many temperatures which we cannot lower in advanced tuberculosis. One reason for this is inexact diagnosis; another, that we have no specific against the enzymes and the products resulting from their action. Would it not be profitable to attempt the production of specific remedies against the body enzymes and the products of their action? This would not seem impossible, for Jochmann and Kantorowicz[9] and others have demonstrated antienzyme in the blood. Our conception of the machinery of immunity is such that we are led to believe that the cells of the body must produce substances which protect the body from these enzymes and the broken-down tissues, which are the products of their action. Our conception is that in these advanced cases, the body cells are constantly producing substances which protect the body against the tubercle bacillus and its toxins and the enzymes and the products of their action; and, where other bacteria are associated in the process, against these. Our rational therapy will be effective only as it aids and supplements these natural processes.

This brings us to the discussion of whether or not tuberculin is applicable in the treatment of fever patients. From a long clinical experience including several hundred fever patients, I am convinced that tuberculin when properly administered is of great value in these cases. The requirements that I would make are a thorough acquaintance with the use of tuberculin, close personal observation, such as is available in an institu-

9. Jochmann and Kantorowicz: Ztschr. f. klin. Med., 1908, lxvi, 153.

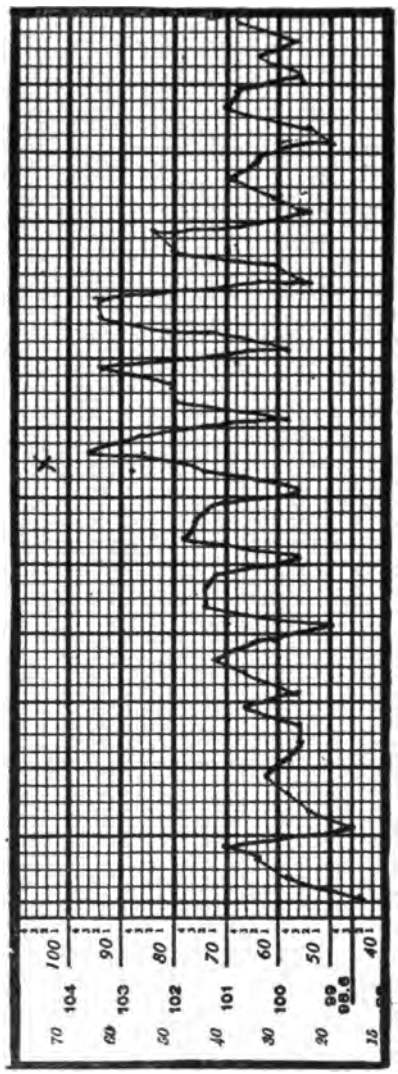


Chart 15.—Fever curve showing elevation in temperature produced by a small ulceration of the pharynx.

tion, and the exercise of care and judgment in the administration of the remedy. I have frequently seen temperatures of 101 and even higher, which were reduced by tuberculin, the fall being coincident with each dose, so as to leave no room for mistake as to the cause. In such instances I have been wont to consider the bacillus and its toxins the chief cause of the rise. On the other hand, I have seen temperatures of less than 100 as well as high ones which seemed entirely uninfluenced by tuberculin. Such, I believe, are those in which absorption of the toxins of other micro-organisms or of the disintegrated tissue are the main cause.

The reason usually assigned for the non-employment of tuberculin in fever is that the patients are already saturated with tuberculin. That this is not necessarily true can easily be established. In the first place, it is probable, as mentioned above, that tubercle toxins are not the chief factor in the production of fever. Again, as noted in a previous paper,[10] if the system of the fever patient were completely saturated with tuberculin, all foci would be the seats of focal reactions which could be easily detected in all visible tuberculous processes such as ulcerations of the larynx and pharynx. But this is not true. Such processes show the focal reactions, however, after injections of therapeutic doses of tuberculin, which, in amount, are short of a fever reaction. Still again, if this were true, all tuberculous foci would break down as a result of the constant focal reactions. Furthermore, if the patient were saturated with tuberculin, the temperature would fall; for excessive doses of toxins would overcome the patient's reactive powers and cause a drop in temperature.

The reason that tuberculin should be employed in the treatment of patients suffering with fever is the same as that for employing it in non-febrile cases; that is, for its effect on the healing of the purely tuberculous processes. There are these in all cases. It must not be supposed

10. Pottenger: Tuberculin as a Therapeutic and Diagnostic Agent, in Hare's Modern Treatment, 1910, 1.

that when a patient has an elevation of temperature the entire portion of the lung that is involved is producing the fever. On the contrary, the area which is the seat of activity is often quite small. I have seen temperatures of from 101 to 105 associated with the formation of small ulcers in the larynx and pharynx where I could feel reasonably sure that these small foci were the cause of the temperature (see Chart 15). The probability of this is strengthened by the elevation of temperature which often follows small abscesses. If the correct administration of tuberculin will not cause an intense and dangerous focal reaction, and when intelligently administered, it will not, then we can see that it can be employed in fever cases with the same advantage to the patient as in non-febrile cases. Of course this statement implies that the patient's reactive powers are still good, and capable of responding in the production of antibodies. Personally I have seen many lungs and portions of lungs which were the seat of recent infection clear out under tuberculin, while the patient ran fever and formed cavities in other portions of the lung. Whoever undertakes the treatment of such patients, however, must not expect tuberculin to do the impossible. He must be satisfied with what it is able to do and not look for miracles. It might do all that it can do and the temperature still persist.

My purpose in this paper is to show the actual as well as contributing causes of fever in tuberculosis and to show what measures may be employed against them and at the same time indicate why we so often fail.

## ABSTRACT OF DISCUSSION

DR. EDWARD F. WELLS, Chicago: The temperature curve in tuberculosis is a matter of great importance from many points of view. Several years ago I had occasion to observe closely a number of cases of early tuberculosis, in which it was clearly shown that a slight or moderate rise of temperature, continuing for about a week, with some local and general symptoms, would be followed by a normal temperature and subsidence of symptoms for about a month. These cycles, each somewhat more pronounced than the one preceding, were repeated with

considerable regularity. These observations were published at the time, and my only object in again calling attention to them is in relation to the practical bearing which they may have on diagnosis by the tuberculin reaction, when the agent is given hypodermically. It is clear that should the administration be made at the inception of one of the febrile periods the height to which the temperature might rise is not a correct measure of the reaction.

DR. NORMAN BRIDGE, Los Angeles: I should like to compliment Dr. Pottenger on the ingenious explanation made regarding the origin of fever in tuberculous patients. I think that he is probably correct. I should like to enter a protest, however, against some of his declarations in regard to the use of tuberculin. He says: "Tuberculin, when properly used, does a great deal of good." I sincerely hope that is true. But I do not believe there is anybody living who can state positively that it is true. I certainly wish that it might be true. To my mind there is no sufficient evidence of the great value of tuberculin. Many have claimed that there is positive evidence of the value of tuberculin; in times past there has been no doubt a great deal of injury done by the use of excessive doses of this agent. Those who are now using this agent should be cautioned. I am positive that it does but a small amount of good compared with the good that results from general hygienic treatment.

With regard to Dr. Pottenger's other statement about the person who knows how to use tuberculin, I should like to enter a gentle and friendly protest, because no man living knows absolutely how to use tuberculin. In my judgment the only real and safe way is to use it in doses so small that it can do no harm; it should be given at intervals so long that no harm can come from the frequency of its administration. Time should be allowed between doses to learn if any harm results from the tuberculin. One should endeavor to learn exactly just the amount of tuberculin to give and the intervals between doses. One cannot generalize from the results obtained in a few cases; one can only generalize from the observation made of a large number—hundreds—of cases of those who have been treated side by side with and without tuberculin. And there are but few men who have had experience enough and have carried their parallel observations far enough and carefully enough to enable them to speak with authority. However, I hope the profession will continue to use tuberculin. I am in the habit of giving 1/500 mg. once a week only. I think that no harm can result from such small doses, but that some benefit will result in some cases. But that the giving of this agent in any case will be productive of great good, I do not believe.

DR. FRANK BILLINGS, Chicago: I supposed that the question of the fever in tuberculosis had been pretty well settled and

that it was due to toxins. Last year while in England I enjoyed a visit with Dr. Paterson, who explained his method of treating tuberculosis by auto-inoculation. Of course I knew something of it before my visit and had seen some of the results of its employment here. If I understand Dr. Pottenger correctly he does not believe that tuberculin in any dose produces or reduces temperature. I simply rise to ask his opinion regarding this point. Were these patients afflicted with the miliary type or the acute ulcerative type?

DR. PHILIP KING BROWN, San Francisco: I also rise to ask a question. I do not understand what Dr. Pottenger means by autolysis in fever in tuberculous patients. This is rather a technical term and difficult to follow in connection with what he says regarding fever in tuberculosis. I have labored under the impression that there was a toxic agent at work which produces fever in this disease. As a matter of fact Dr. Vaughan made some interesting experiments, reported before the Association of American Physicians last summer, on the protein reaction as a cause of fever in bacterial diseases. The animal experimented on could be caused to have temperature of any type by the introduction of some protein substance subcutaneously. Most of the work was done with egg albumin. Dr. Vaughan explained the resulting fever as depending on some anaphylactic action. The extent of this reaction depended on the frequency and the amount of the protein introduced. I should like Dr. Pottenger to state whether he had gone into this carefully and what he means by stating that toxins do not cause or increase the fever.

DR. C. F. TENNEY, Toledo, O.: I have given tuberculin with beneficial results when the temperature has not been above 99.4 F. If the temperature is higher than 99.4 F. I believe that rest is indicated. I should like to ask Dr. Pottenger why he gave tuberculin when there was a high temperature.

DR. F. M. POTTENGER, Monrovia, Cal.: If I had been permitted to read my paper in full the various questions asked me would most probably have been satisfactorily answered. Dr. Bridge has certainly been unfortunate in his experience with tuberculin. I wish to state emphatically that I do not agree with what Dr. Bridge has stated regarding the use of tuberculin. The intelligent use of tuberculin, like all other remedies, consists in individualization, suiting the dosage to the individual patient under treatment. When one uses tuberculin after the manner described by Dr. Bridge, unsatisfactory results are sure to follow. One does not operate in any two cases of appendicitis alike, or treat any two patients with typhoid fever the same, neither does one administer digitalis nor strychnin alike in all cases, and yet Dr. Bridge would have us give 1/500 mg. of tuberculin once a week to all patients who are treated with tuberculin. I would not want to have it go out from this meeting that this is the proper use of tuberculin. Such a method is erroneous and incapable of producing the best results.

For fifteen years I have preached the importance of individualization in the use of tuberculin. To give so many drops of this or that dilution at certain intervals cannot be expected to be productive of much good. One must bear in mind what tuberculin is and what it is supposed to do. Unless great care is used in its administration much harm may result, but when used intelligently good must just as necessarily follow.

When tuberculin is being used all other measures which are recognized for building up the patient should be employed.

Tuberculin can be employed as intelligently as any other remedy that we have. We cannot give a satisfactory explanation of the action of many of our remedies, but this must not deter us from using them according to our clinical observations. Small doses of tuberculin are not necessarily conservative. The proper method of using tuberculin is to give the right dose at the right time. If one starts in with small doses and increases them gradually, the patient will soon bear the doses without danger of reaction. In my private work I always have more than 100 patients under treatment with tuberculin and yet I rarely have a rise of temperature of more than ½ degree as a result of its administration. I agree with Dr. Bridge that no one knows exactly how this remedy acts. Who knows all about digitalis or strychnin? Our lack of knowledge, however, does not deter us from producing good results.

Dr. Billings speaks of the work of Paterson. I am familiar with Paterson's observations and think he is doing an admirable work, but it must not be forgotten that he is dealing exclusively with early inactive cases. The patients of whom I am speaking are almost all advanced and suffering from active tuberculosis. Rest is an absolute essential in the treatment of all cases of active tuberculosis. I always enforce it if the temperature is above 100, and in many cases in which it is under, if other conditions would indicate it.

Regarding Paterson's interpretation of every rise of temperature following exertion, as an auto-inoculation, I think there is some room for question. I do not believe that all these can be ascribed to an auto-inoculation of tuberculin. There are other factors which come in.

Regarding the effect of large doses of toxins in reducing temperature, many experiments have been performed in which staphylococci and streptococci as well as tuberculin have been employed, showing that following the injection the temperature was markedly decreased, and if the dose is fatal the animal dies with subnormal temperature.

In reply to Dr. Brown regarding enzymes and autolysis, I would refer him to the excellent work done by Frederick Muller, Ascoli and Bezzola, and Opie. From my clinical experiments I believe that enzymes and the products of autolysis are very important factors in the production of fever and that they deserve very careful study.

# THE LEUKOCYTOLOGY OF TYPHOIDAL DISEASES, AS A GROUP-PHENOMENON WITHIN THE TYPHOID-COLON FAMILY OF BACILLI (TYPHACEÆ)

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Typhoid and paratyphoid bacilli, the bacillus of Gärtner, the paracolon, colon and dysentery bacilli belong to one family.[1] Botanically, they are branches of one tree. There are no permanent, fundamental, cultural[2] or morphologic differences between them.[3] The identification of a single member of this group by any special culture-medium has not been realized. The primordial kinship and common ancestry of these allied germs is demonstrable in many ways. It is only by acquired or biochemical properties that members of this group differ from each other. The Widal reaction, as Durham first showed, is only electively specific, not strictly so in the sense of Widal's and Buchner's words. The teaching of exclusive specificity in medicine produced not only passive, *laissez-faire* clinicians and therapeutic nihilists, but also a crop of specific public hygienists. Pasteur's conception of a specific pathogenic agent for infectious diseases shows the inspiration of a genius, Richet's anaphylaxis and Bordet-Gengou's complement deviation are of incontestable benefit to mankind, but somehow these several discoveries have not accomplished what they

1. Vallet, G., and Rimbaut, L.: Les bact. intermédiares de la famille Coli-Eberth, Arch. de méd. expér., March, 1910, xxii, No. 2.
2. Rubener: The Importance of Paratyphoid Bacilli, Berl. klin. Wchnschr., June 13, 1910, p. 1908.
3. Müller, Reiner: Ueber Paratyphus, Deutsch. med. Wchnschr., Dec. 22, 1910, p. 2397.

seemed to promise. The conditions under which a germ of a given group becomes pathogenic for man are as yet very obscure; even the rules of immunity as applied to anaphylaxis stand on their head.[4] It is certain that our reasoning on the ground of the strictly specific pathogenesis of germ diseases is too narrow. Anatomic and clinical phenomena do not justify the strict separation of typhoid and paratyphoid fevers.[5] Their epidemiology belongs together.[6]

I believe that the epidemiology of all infectious diseases, their morbidity and mortality statistics, their pathogenesis, their pathology, and clinical manifestations will be better understood when we shall study them collectively by groups, rather than individually. Just as in qualitative chemistry, there is shown in qualitative bacteriology[7] a distinct arrangement into botanical families. The law of periodicity of elements as propounded by Mendeleeff[8] in 1869 is applicable to the realm of microorganisms. Even now the laws of chemistry begin to dominate bacteremic processes.[9] That such reasoning is logical is proved by the following:

Germs, like chemical elements, can be arranged into definite groups, because, first, their individual members are morphologically similar; second, they feed or may eventually be made to feed[10] on the same culture-media; third, they show a distinct racial attitude toward oxygen and nitrogen; and fourth, their biochemic products bear plainly the stamp of family-reactions, as proved by Pfaundler's co-agglutinins, and by their leukocytic

4. Besredka, A.: Anaphylaxis, Handbuch der Immunitäts-Forschung, 1911, Supp. vol. i.

5. Rolly, Fr.: Zur Paratyphus Frage, München. med. Wchnschr., March 14, 1911, p. 556.

6. Bainbridge, F. A.: Epidemiology of Typhoid and Paratyphoid Fevers, Proc. Roy. Soc., February, 1911, iv, No. 4.

7. Jackson, D. D.: Classification of the Bacillus Coli Group, Jour. Infect. Dis., March 6, 1911, p. 246.

8. Mendeleeff, D. I.: A Conception of Ether, St. Petersburg, 1869, New Translations by George Kamensky, London, 1905.

9. Horovitz, A.: Biochemical Rôle of Bacteria, Arch. d. Sc. biol., St. Petersburg, 1910, xv, No. 1.

10. Bradley, Burton: Biochemical Characters of the Bac. Typhus, Proc. R. Soc., February, 1911, iv, No. 4, p. 48.

reactions. Andrewes[11] has found that guinea-pigs are co-sensitized toward paratyphoid germs and colon bacilli by previous injections of typhoid bacilli. From the standpoint of histochemistry and histopathology the classification of infectious diseases into groups suggests itself. The serum and tissue reactions of the typhoid-colon group, of the anaerobic intestinal flora, and of the streptopneumococcus family are group phenomena. The leukocytology of these infections furnishes the biochemical proof of the generic kinship between the members of these bacterial races. Clinically, this grouping of infectious diseases is very striking and, in my opinion, constitutes another proof of the existence in nature of the cyclic or periodic arrangemnt of germs — of living, organic molecules — parallel to that discovered by Mendeleef in regard to chemical elements. It is not unlikely that the teleological scheme of this grouping exists for the induction, maintenance and consumption of the circulation of elements within the human body. The generic, racial or electively specific activity of the typhoid-colon group is spent on the growth and the decay of the protein molecules in the intestines.[12]

As to whether infection and immunity in man show evidences of an evolutionary or mutating character of germs, and of their reactions on the host, I cannot discuss at this time. Suffice it, now, to take up the present status of pathogenesis, and clinical and epidemiologic significance of the leukocytology of typhoid and paratyphoid fevers.

My object in writing this article is, first, to enounce and promote the group study of typhoid infections; second, to show why we should suspect and diagnose them earlier than hitherto; third, to discuss the part played by the tissue-cells in the production of group-characteristics versus the specific theory of one indi-

11. Andrewes, F. W.: The Leukocytes in Infection and Immunity, Lancet, June 25, 1910, p. 1739.

12. Fisher, Van Loghem Citing: Varieties of Typhoid and Allied Bacilli, Centralbl. f. Bacteriol., Feb. 1, 1911, lvii, No. 5.

vidual germ; and fourth, to revaluate the significance of the Widal reaction.

The study of the individual members of the typhoid, paratyphoid colon group has demonstrated a marked discrepancy between the morbidity and mortality statistics of these affections. Indeed, Hazen's[13] theorem of the Mills-Reinke phenomenon is an attempt to cover up this breach in the epidemiology of these water-borne diseases, the generic relation of which was recognized by a layman before clinicians thought of it. The classification of water-borne and food-borne diseases, however, should be based on clinical evidences mainly.[14] The early bacteriologic diagnosis serves essentially to identify the group to which the germ belongs,[15] cultural tests being insufficient and serologic reactions occurring late in the disease. In order to diagnosticate a case of typhoid or paratyphoid infection early we must suspect it earlier, that is, even before clinical evidences have become manifest. In typhoidal affections the preclinical symptoms consist in the bacillemia and the leukocytic changes, which, presupposedly, must have existed for some time, perhaps for two or three days, before the onset of any subjective symptoms. If at all applicable, the curative vaccine therapy[16] or the medical abortive treatment of typhoid fevers must be applied very early to induce bacteriolytic immunity, in view of the absence of antitoxic and phagocytic antibodies as observed by Vaughan and his school.[17] The end of the first week of typhoid fever is called the diagnostic stage by O. Naegeli.[18] It is then that the leukocyte counts are

13. Sedgwick-McNutt: The Mills-Reinke Phenomenon, Jour. Infect. Dis., Aug. 24, 1910, p. 489.
14. Brion, Arthur: Typhus-Paratyphus, Modern, Clinical Medicine, 1910, p. 60.
15. Rolly, Fr.: Diseases Produced by the Paratyphoid Bacilli, Deutsch. Arch. f. klin. Med., 1906, lxxxvii, p. 595.
16. Richardson, W. W.: Treatment of Typhoid Fever, Mass. Gen. Hosp. Rep., 1908-1909, ii, 97.
17. Vaughan, V.: The Specific Treatment of Typhoid Fever, Am. Jour. Med. Sc., September, 1908, p. 330.
18. Naegeli, O.: Ueber das Erkennen Typhus-ähnlicher Krankheiten, etc., Cor.-Bl. f. schweiz. Aerzte, 1902, xxxii, 109.

most valuable, as I have shown before.[19] The early stage of all typhoid infections is the most infectious, because the germs are very numerous in the circulating blood and excreta during the first stage of the disease.[20]

Typhoid bacillary sensitization is a protein poisoning. The manner of the intoxication, rather than its nature, determines the peculiar lymphoid tissue and leukocytic changes of typhoid fevers. The tissues furnish the characteristic reactions rather than the germ, and they do so in accordance with the manner in which the alien protein is brought in contact with them. This would account for the clinically polymorphous character of typhoidal and paratyphoid affections. Laurent[21] holds that the number of successive generations of bacilli decide on the severity of the infection. It is probable that the negative phase of antityphoid vaccination,[22] the negative phase of leukopoiesis in rabbits, as observed by Andrews, and the incubation of typhoid fevers in man are illustrations of one and the same process.

The revaluation of the Widal test is imperative. This reaction is less specific than formerly believed, but its scope is widening since Pfaundler's work. Its late appearance is its chief drawback, and, owing to the indefinite onset of the disease, an early Widal reaction should always be viewed with suspicion.[23] Its value as a means of group-diagnosis has increased, while in specific diagnosis it has admittedly lessened. The pre-Widal diagnosis of typhoidal diseases should be the rule, not the exception. Paratyphoid affections are seldom recognized in practice and are often classed as ptomain

19. Hultgen, J. F.: The Pre-agglutination Diagnosis of Typhoid and Paratyphoid Fevers, Tr. Chicago Pathol. Soc., August, 1909, p. 270.
20. Von Ivigalski and H. Conradi: Ztschr. f. Hyg. u. Infect. Krankh., 1902, xxxix, 298.
21. Laurent, E.: Virulenz-Problem der pathogenen Bacterien, Fisher, Jena, 1910.
22. Vincent, H.: Typhoid Vaccination, Bull. d. l'Acad. de méd. de Paris, Jan. 24, 1911, p. 63.
23. Drysdale, J. H.: The Agglutination Reaction, Allbutt's System of Medicine, 1905, i, 693.

poisoning, gastric fever,[24] mucous gastritis[25] or walking typhoid fever. The existence of intermediate forms of the typhoid colon group, the insensible gradations from the bacillus of Eberth to the bacillus of Escherich, and the exceedingly important pathogenic, hematologic, epidemiologic and clinical characters, varying in crescendo or diminuendo with the distance of a given germ from the top or the foot of his family tree, is unfortunately but little known in medical books.

The incentive for this work grew on me in the course of the last six years, while making routine blood examinations on all of my patients. The value of careful hemanalyses[26] has been recognized by several authors, especially in differential diagnosis.[27] Other reasons impelling me in this line of investigation were the following considerations: Clinically, it is characteristic of the members of typhoid-colon dysentery group to produce ulcers, owing to the lymphotoxic effects of their poisons. While the ulcers of typhoidal and dysentery group show a distinctly segmental intestinal localization, the colon bacillus produces ulcers of the stomach (F. B. Turck), appendix and large bowel. The higher in the scale of this group a given bacillus is, the longer the incubation, the greater the crescendo of negative leukopoiesis, the more marked the immunity, the less the facultative saprophytism and the more pronounced the clinical condition known. I am referring to the bacillus of Eberth. With a preliminary generalizing survey of the typhoid-colon group it will be easier to understand the leukocytology of typhoid and paratyphoid fevers. The diagnostic and prognostic significance of complete successive blood-counts will then explain itself. It is to be hoped that cytology may clear a situation which has lasted for thirty years, and for which twenty years of

24. Schlegelmann, Albert: Febris Gastrica, München. med. Wchnschr., 1911, No. 6, p. 299.
25. Schneller: Febris Gastrica, München. med. Wchnschr., 1911, No. 10, p. 515.
26. Cabot, R. C.: Differential Diagnosis, Phila., 1911, p. 406.
27. Tompkins, McGaw: Atypical Onset of Typhoid Fever with Report of Cases, Old Dom. Med. Jour., March 19, 1911, xii, No. 3.

humoral pathology have not accounted. Typhoid fever does not spontaneously occur in lower animals. The typhoid peritonitis of guinea-pigs is no parallel to typhoid fever in man.[28] Experimental bacteriology is of little use here. Combined bedside and leukocytic data furnish the safest basis for clinical reasoning and for a correct attitude toward the pathogenesis of infectious diseases. The leukocytology of typhoid and paratyphoid fevers is another proof for the distinct generic relations between the members of this group. It throws light on the reciprocal relation between incubation and immunity. The pathogenesis of the typhoid blood-picture must not be ascribed to the endotoxins *per se*, but to the lymphoid tissue reactions which they call forth. Any chronic tissue lymphocytosis may produce a similar blood-picture, for instance, the first stage of tuberculosis and splenic anemia. The generalized endothelial and lymphoid cell hyperplasia described by Mallory,[29] Edsall, Longcope[30] and others and observed by Virchow, depends on the manner of intoxication, rather than on the nature of the intoxicant. Indeed, the colon bacillus produces a disease not only clinically identical with typhoid fever, as Coleman and Hastings report,[31] but also with the blood-picture as that observed in Eberthian infection.

The material for the present report consists of cases of typhoid and paratyphoid fever in my private practice and from the Englewood Hospital. The patient's leukocytes were examined every two or three days during the course of the disease. In this way I was able to secure from two to ten and twelve total and differential leukocyte counts for each day, with the exception of the first two days. This is, of course, quite excusable in view of the usually insidious and indefinite onset of typhoid fevers. From the literature I could gather only total white blood-counts, differential analyses being so rarely

28. Metchnikoff, E., and Besredka, A.: Recherches sur la Fièvre Typhoïde Expér., Ann. de l'Inst. Pasteur, March, 1911, No. 3.
29. Aschoff: Pathological Anatomy, 1909, ii, 353.
30. Longcope, Warfield: Rep. Ayer Clin. Lab., March, 1905.
31. Coleman, Warren, and Hastings, T. W.: Bacillus Coli Communis, Am. Jour. Med. Sc., February, 1909, p. 199.

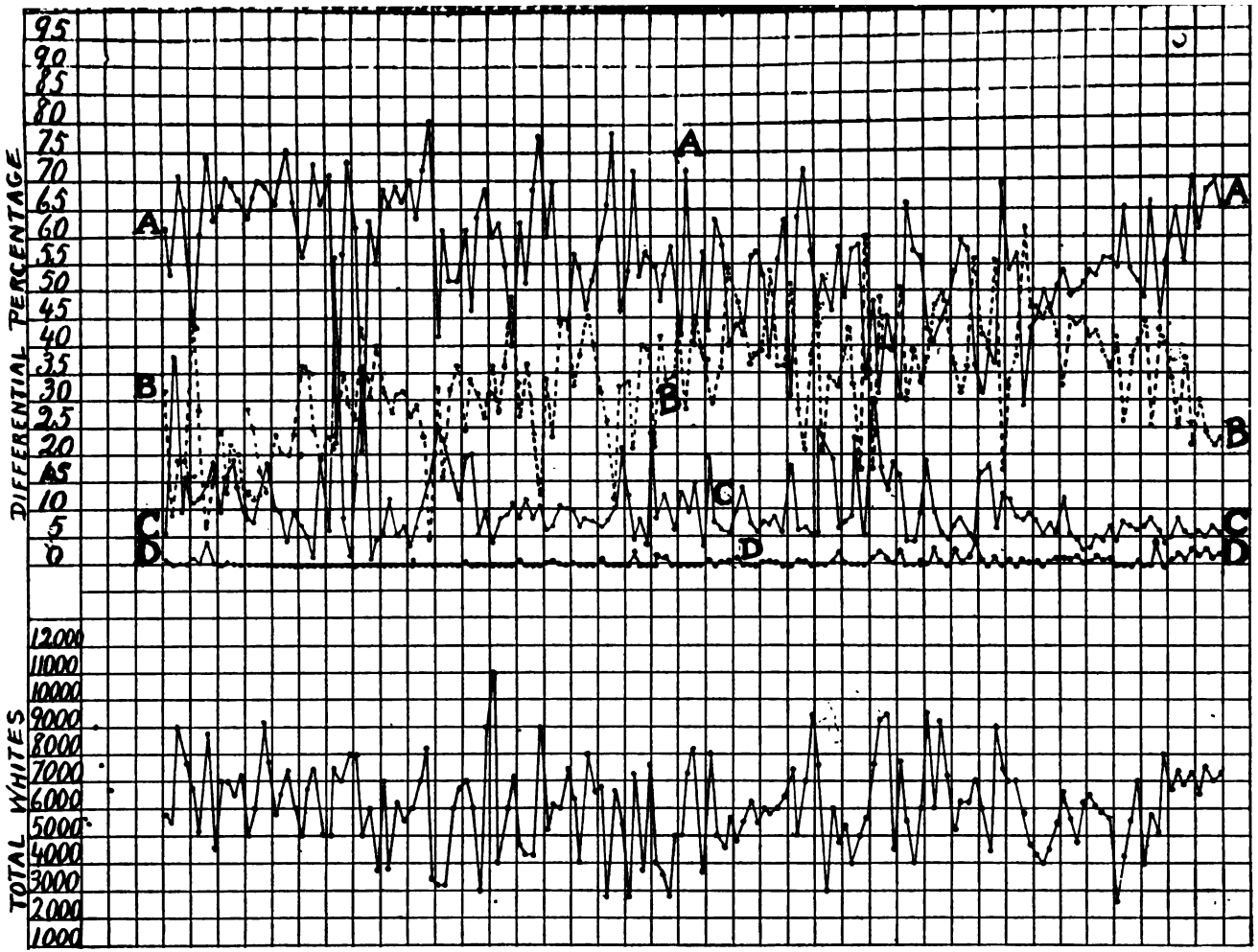


Chart 1.—The leukocytology of ortho-typhoid fevers. Four counts from each day for six weeks, obtained from thirty-six patients in private practice. A indicates polynuclears; B, small mononuclears; C, large mononuclears; D, eosinophils.

and poorly made that I had to abandon their use in this report. As many blood examinations were made as the patients and circumstances would allow. Arneth's method of establishing by nucleo-analysis a polynuclear blood-picture was not used, although most of the writers in this country follow this investigator. I consider it very important to examine *in toto* the white blood-life of the patient, by estimating the hemoglobin, securing the total leukocyte number, and dividing the white cells into four classes, the polymorphonuclear, the small mononuclears, the large mononuclears with the transitionals, and the eosinophils. The basophils were omitted as of little value. Care was taken not to make the blood-specimen right after a cold bath or cold sponge as Winternitz and Thayer cautioned.[32] The following nomenclature was thought more accurate, more simple and descriptive than either Arneth's[33] or Sondern's. For the total number the terms "normocytosis," "hypercytosis" and "hypocytosis" were used. In the differential counting I arranged the white cells into the polynuclear, mononuclear, mixed or di-cytosis, according to the percentages of either the polynuclears or mononuclears, or of both, being above or below the normal proportions. The reasons for this I have explained elsewhere.[34] The normal blood-picture being a dinormocytosis, I was able to establish the leukocytic alterations during the entire course of typhoid and paratyphoid fever. The physiognomy of this continual blood-picture may be summed up as follows:

Polynuclear hypercytosis (several hours, probably).
Polynuclear normocytosis (probably lasts only a day).
Polynuclear hypocytosis (up to 10-15th day).
Di-normo-hypocytosis (10-15-18th day).
Mononuclear hypocytosis (15-25th day).

32. Thayer, W.: Increase in Leukocytes Following Cold Baths in Typhoid Fever, Bull. Johns Hopkins Hosp., April, 1893, No. 4, p. 30.
33. Arneth, J.: Blutuntersuchungen bei Tuberculosis Pulmonun., München. med. Wchnschr., 1905, No. 12, p. 542.
34. Hultgen, J. F.: Mixed Hypercytosis, Its Nature and Significance, Quart. Bull. Northwestern Univ. Med. School, December, 1910, xxi, No. 3, p. 163.

**Mononuclear normocytosis (20-30th day).**
**Mononuclear hypercytosis (25-35th day).**
**Mixed or di-hypercytosis (30th-45th day).**
**Di-normocytosis (40-50th day).**

Charts 2 and 3 are arranged schematically. Chart 1 illustrates the comparative constancy of a typhoidal blood-picture, persisting in spite of the well-timed shifting of its ingredient leukocyte-curves. The blood-picture of typhoid and paratyphoid is typical during the entire course of the disease. Its differential diagnostic value is as great in the fourth week as in the first week. It goes without saying that these total and differential leukocyte-curves represent the movements of the leukopoietic tissues (lymphoid cells, spleen and bone-marrow). As such their great prognostic value becomes self-evident.

A few preliminary remarks on the leukocytology of these kindred affections:

It is, of course, natural to accept the fact that in short duration, abortive or walking typhoid (see Chart 3) or paratyphoid fevers the leukocyte picture shows curves which are much shorter, though otherwise identical with those seen in true typhoid fever. It is also easily conceivable that the cytology of these infections in children would be tinged with the attributes of youth —resiliency, if not exuberance. Hence the shorter course and the greater intensity of blood-life, more lymphocytosis, relative and absolute, a lesser and shorter leukopenia and more marked mixed hypercytosis. Youth, health and the intensity of the existing affections must be considered in the framing of the typhoid-paratyphoid blood-picture. In judging the diagnosis or the prognosis, it is essential to base our opinion on the conjoint clinical and hematologic examinations.

### THE INTERPRETATION OF THE TYPHOID-PARATYPHOID BLOOD-PICTURES

After a slight (supposed) initial rise, the total leukocytes drop rapidly and maintain a fairly constant low level until the fifth and sixth week of the disease, when,

in juvenile patients or in patients with resilient blood-forming system, they return toward normocytosis, which yield to a more or less transitory mixed leukocytosis and then gradually shifts to a permanent normal level. As to whether these total white-cell changes are due to negative chemiotaxis according to Ehrlich, or due to a typhoid-endotoxin inhibition of the bone-marrow as O. Naegeli believes,[35] cannot as yet be definitely decided on. That the leukocytes are screened in the lung capillaries, as Bruce, Jacob Goldscheider and Andrewes maintain, is a hypothesis to which I cannot

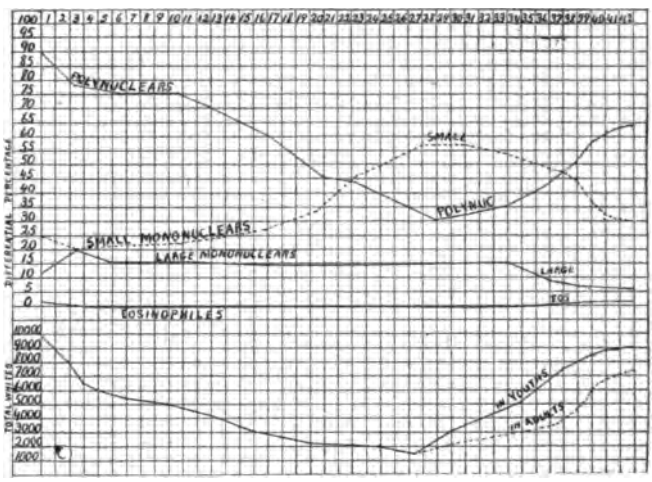


**Chart 2.—"Leukocytology of orthotyphoid fever (schematic)."**

adhere. The leukopenia of typhoid affections looks to me like the prolonged ebb of the functional wave of cell immunity, a form of an hematopoiesis characterized by slow production and slow maturation of leukocytes. The polymorphonuclear cells after a probable initial rise diminish at first rapidly in number, then lose gradually but constantly until the end of the fourth week (see Charts 1, 2 and 3), when they return step by step toward the normal percentage. The polynuclear curve crosses

35. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, 1908, p. 427.

the mononuclear wave twice, first on its downward course about the twenty-second or twenty-fourth day, and again on its ascent by the beginning of the seventh week. The small mononuclear leukocytes or lymphocyte curve is the exact counterpart of its predecessor polynuclear.

Their movements are always complementary and compensatory. The lymphocytes rise after a slight initial drop, then move at a fairly even subnormal level until the fifteenth or eighteenth day, when they approach and cross their normal line, remain above normal for eight

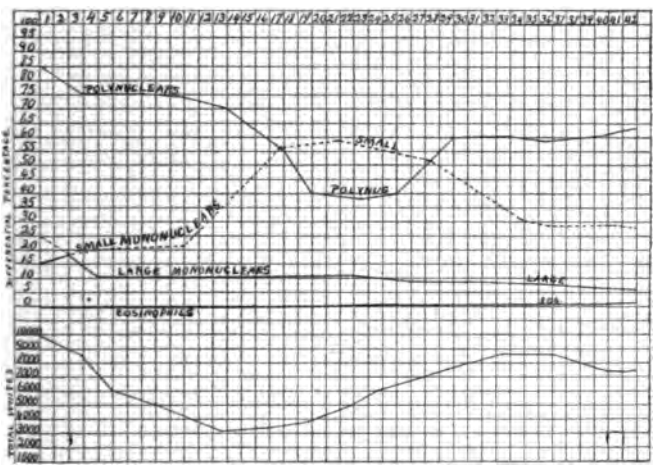


Chart 3.—"Leukocytology of paratyphoid fever (schematic)."

or ten days and then recede gradually into their normal proportions.

The large mononuclears and transitional cells form the most interesting part of the typhoid blood-picture. They are remarkably increased in number up to the end of the sixth week, then they regain their normal percentage. This myelemia, as Pappenheim calls it, was observed by Chetagurow in 1889. The resemblance of their curve to the polynuclear wave is, in my opinion, a very remote one, although Naegeli believes them to "follow the neutrophils mostly." There is no other prolonged leukopenia known to me in which there is such

a continually high proportion of large mononuclears. This phenomenon I believe to be explainable in three ways: by a slow maturation of these cells into polynuclears, by their overproduction from the endothelial cells of the lymphoradicles, or by both conjointly.

The eosinophils undoubtedly play an important rôle in typhoid fever cytology. I fully agree with Naegeli's dictum that "no febrile disease can be of typhoid nature if the eosinophils are present in normal or half-normal proportions." These cells disappear suddenly and totally, and return very cautiously around the beginning of the sixth week.

CONCLUSIONS

1. There exists a typical typhoid and paratyphoid blood-picture throughout the course of these diseases.

2. This blood-picture is characteristic of the obligate parasites of the typhoid-colon group and constitutes, probably, the counterpart to that usually found in colon bacillus infections.

3. The leukocyte reactions of typhoid and paratyphoid infections must be interpreted as group-phenomena.

4. In the pathogenesis of this typhoid-paratyphoid blood-picture, the germs and lymphatic tissues play a joint rôle, but the character of the intoxication determines the blood-picture.

5. The diagnostic value of the leukocyte-picture is particularly great during the first ten days, while its prognostic value is especially marked in the last ten or fifteen days of the disease.

6. Repeated, combined total and differential leukocyte-counts must be made throughout the course of typhoid or paratyphoid fevers. The cytology of these affections can be appreciated in no other way.

7. The immunity with leukopenia of the typhoid-paratyphoid group and the immunity with active leukopoiesis of the colon wing of this family are evidently the two extreme phases of one fundamental process.

8. Blood-charts and reasoning by analogy show that the conception of the typhoid blood-picture as a group phenomenon within the typhoid-colon family is correct.

9. Each member of the typhoid-colon bacillus group is able to produce either a toxic gastro-enteritis or a true typhoid affection.

10. The close or fundamental kinship between the numerous members of the typhoid-colon group of bacilli is proved, first, clinically by the time-honored name of typhoid fevers, second, pathologically by their common faculty of producing ulcers in the gastro-intestinal tract, third, cytologically by their blood-picture, fourth, serologically by the coagglutination of Pfaundler, fifth, epidemiologically by Hazen's theorum of the Mills-Reinke phenomenon of typhoid and general mortality.

11. The law of periodicity of inorganic chemical elements, enounced by D. I. Mendeleeff in 1869, is in my opinion applicable to the distinct group-arrangement of organic, living microorganisms.

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# THE IMPORTANCE OF THE QUANTITATIVE REGULATION OF THE DIET

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It will generally be admitted that modern methods of infant-feeding have been of very great benefit. It is one of the very few accomplishments in dietetics that the profession may point to with pride. Yet it differs from the older methods of milk feeding chiefly in the fact that the nutritive ingredients of the milk are regulated quantitatively with greater accuracy.

Our grandmothers used to dilute cow's milk in giving it to infants. Their object was to make the milk "less rich" and more digestible, with fewer "curds." They were in reality lowering the percentage of protein, which in cow's milk is too high for infants. Then they sweetened it, apparently to make it more acceptable to the taste. But this also fulfilled the very desirable object of increasing the carbohydrates, which are low in cow's milk as compared with human milk. And further, if the baby did not gain in weight they used "richer" milk, that is, they increased the percentage of fat in the milk mixture, thus adding materially to its nutritive value.

So "modified milk" and "percentage feeding" are not new methods—for milk was always modified—but they represent the introduction of accuracy in the quantitative regulation of the infant's food. It has accomplished so much that at first sight it seems hard to believe that the great advance in infant-feeding is based essentially on so simple a thing as greater accuracy, yet this really

is the case. The explanation lies in the fact that this accuracy permits the physician to regulate the amounts of the different foodstuffs—protein, fats and carbohydrates—which comprise the nutritive part of all food. He can do this with sufficient accuracy to allow him to study the effects of such modification of the amounts of the different foodstuffs, and to adapt the diet intelligently to meet the requirements of the individual case. The method needs no defense from us; our object is to use its well-known success as an argument for the extension of the same principle to other fields—to the regulation of the diet of adults in all cases in which greater accuracy will be advantageous.

In general, the regulation of the diet of adults by physicians is not a matter in which the profession can take much pride. With a few directions of "Do take this" and "Do not take that"—the selection of the foods being largely regulated by tradition based on empiricism—the physician leaves the rest to the patient's appetite and the judgment of a nurse or some lay person. This is equivalent in infant-feeding to the direction: "Feed the baby milk"—leaving all other details for the family to work out. It is essentially an absurd position, which is perpetuated by two factors. One is the lack of appreciation by physicians of what may be accomplished by more scientific diet regulation; the other is the difficulty of its application in their hands. This is due largely to the fact that the present generation of physicians was not taught the fundamental facts with any reference to their practical application. This latter defect will soon be remedied, for the importance of the scientific regulation of the diet is being more fully recognized by the profession. The medical schools are beginning to give instruction along these lines, and the coming generation of physicians will be prepared to utilize these valuable measures fully. Even now its value in the treatment of disease has been proved, and an important question for the older physicians to decide is whether they will "keep

up with the procession" by adopting this advance in dietetics, or will wait for the more efficient youngsters to crowd them to one side.

You need but to mention the word "diabetes" to the wide-awake physician of to-day and he will recognize that these remarks apply to this disease at least. He knows that the most successful treatment of this disease is based on the careful quantitative regulation of the amounts of carbohydrates allowed in the diet, combined with such an adjustment of the other foodstuffs as to furnish sufficient nutriment for the needs of the system.

The old haphazard methods of treating this disease are no longer justified. Our duty to our patients demands the quantitative regulation of the amount of carbohydrates given in the treatment of diabetes, and the recognized importance of this measure is again cited by us as an argument for the extension of this measure over a wider field.

It has not so generally been recognized that the proper regulation of the amount of protein in the food is almost as important in the treatment of nephritis as is the regulation of the carbohydrates in diabetes. Yet, all will admit that the fundamental principle of the treatment of this disease is to spare the kidneys from unnecessary work. Since one of the chief functions of the kidneys is to eliminate the waste products of nitrogenous metabolism it necessarily follows that we can secure this result best by limiting the amount of the nitrogenous material, or protein, that is taken in the food. This matter has been emphasized by Von Noorden and others, and an article by one of us, delivered before this Section last year, dealt with this matter at length.[1]

A further reason for the quantitative regulation of the diet in diabetes and nephritis is the fact that it is not only necessary to reduce the amounts respectively of carbohydrates in the one case and of protein in the other, but that it is of equal importance to make sure

1. Arnold, H. D.: The Importance of a Low Protein Diet in Chronic Nephritis, THE JOURNAL A. M. A., Dec. 24, 1910, p. 2193.

that the patient is getting a diet of sufficient nutritive value to meet the requirements of the system for heat and energy and to offset tissue waste. Unless this is provided for we add insufficient nutrition or partial starvation to the condition of disease already existing. This can best be determined by a calculation of the caloric value of the diet. In order to ascertain this we must know with some approach to accuracy the amounts of food taken, which is another way of expressing the quantitative regulation of the diet.

In another field this same consideration holds. Whenever the heart is affected the question of a sufficient supply of nutriment to enable it to maintain its strength is of vital importance. Unless there is sufficient nourishment the heart-muscle will weaken, and disastrous results will follow. This is of the greatest importance in the so-called reduction cures for obesity. If in these cases the heart is not strong, as is often the case, serious and even fatal damage may be done to the heart by cutting the food down too far or too rapidly. In such cases the reduction can be done safely only when the nutritive value of the diet is followed closely. Furthermore, it hardly needs to be argued that in any system for reducing the weight the quantitative regulation of the diet will enable the physician to study the case more intelligently and to get more satisfactory results than if this measure is neglected. This is true whether there is any danger from the heart or not.

In many cases of apparent neurasthenia and debility or malnutrition we have found that a calculation of the diet not only helps in the understanding of the case and in the diagnosis but points the way to treatment and enables us to give a more accurate prognosis.

It is interesting to note that recently the diet in cases of tuberculosis has been the subject of extensive study from this point of view. It has been proved that patients do as well or even better when such study and quantitative regulation provides a well-balanced diet,

with an abundant but not excessive amount of nutriment.

In gout and those forms of rheumatism in which metabolism is at fault the quantitative regulation of the food is important. These conditions are not as yet as well understood as we might wish in these respects, but this method will enable us to give more scientific consideration to the problems which these diseases bring up. In this way we may hope for a better chance for a successful solution of these problems. In both diseases the cutting down of the protein of the diet seems advantageous, and in gout that careful regulation of those articles of food that contain purin bodies, which is an essential feature of the treatment, can best be secured by the quantitative regulation of the diet.

We have pointed out a number of conditions in which the quantitative regulation of the diet will be of aid and in many cases it is essential to successful treatment. Few will deny the desirability of such measures. The question arises whether it is practicable in application. In order to carry out these measures we must know with some accuracy the composition of food and we must understand a few of the fundamental principles of dietetics. Fortunately, the more recent books on treatment have taken up these matters in some detail. With some patience and study the matter can be worked out. In many of the diseases mentioned, the text-books or monographs will give the desired information. At first, the work is difficult and time-consuming, because it is new and is more or less complicated, but familiarity soon brings facility, and the results well repay the time and trouble involved. We have used the diet chart prepared by one of us (Arnold) in practice for several years and have found that it simplifies the problem a great deal, and makes it feasible to do this work in private practice satisfactorily, when once the physician is conversant with the method of its use. We have repeatedly found that an intelligent nurse can use these charts not

only to record, but to calculate the diet, and this has been done also by intelligent members of the family of the patient. Such reports enable the physician to follow his case with little trouble and to handle it much more intelligently. These charts are published by the W. B. Saunders Company. They are not essential for this work, for all that is essential is for the physician to get his data from any reliable source and he can apply them in any convenient form. Such charts merely bring convenience in such methods. With such an aid we have found it perfectly feasible to carry out this work in practice. From an extended experience with this work we can say with confidence that it is well worth while in any condition where the diet enters as an important factor in treatment. By such means we raise dietetics from unintelligent empiricism to a fairly satisfactory scientific basis.

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## ABSTRACT OF DISCUSSION

DR. WILDER TILESTON, New Haven, Conn.: The quantitative regulation of the diet is of extreme importance in the treatment of all conditions of undernutrition and obesity. It is not at all difficult to regulate the diet in this way if one obtains tables showing the nutritive value of foods. Such tables can be obtained from Bulletin 28 of the Department of Agriculture, on the payment of 10 cents. The principles governing the diet of the ill are frequently misunderstood and misapplied—more so than other principles in medicine.

# LABORATORY DIAGNOSIS OF SYPHILIS *

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Laboratory aids to the clinical diagnosis of syphilis have developed rapidly since the announcement by Schaudinn and Hoffman[1] in 1905, of the *Treponema pallidum* as the probable causative agent. Prior to that time the rarely used Justus test (increase of hemoglobin after the administration of mercury) was the only laboratory procedure. A subject so vast and important can be approached from many sides, the more important being the technical, clinical and experimental. Therefore, it will be necessary to limit this paper to those of more general and practical use, and to avoid long technical descriptions; in other words, to present to the general practitioner the value and limitations of the various laboratory methods, rather than to dwell on the means of carrying them out.

## SMEARS

This was the first method used generally for the purpose of demonstrating the presence of the *Treponema pallidum*. Many stains and mordants have been used. These divide themselves into two general groups: first, the more intense anilin dyes together with various mordants and, second, various modifications of the Romanowsky stains. I find the following method exceedingly satisfactory, but I do not wish to be considered as limiting the satisfactory methods to the one described.

* From the Serological Laboratory, University of California Hospital.

1. Schaudinn und Hoffman: Arb. a. d. k. Gsndhtsamte., 1905, xxii, 527.

The smears are first fixed in the fumes of osmic acid, then immersed in a weak solution of potassium permanganate as a mordant, washed in distilled water and covered with Giemsa stain diluted 1 to 10. They are heated on a copper plate for twenty minutes; the slides are then washed in distilled water and dried in the air.

By this method the treponemas are stained a deep purple.

Stearns' silver method stains the treponema a deep black but distorts their outline somewhat. In addition, it is very difficult to obtain a solution of silver nitrate that will not precipitate a granular film on the smear.

Another method generally used on account of its extreme simplicity and rapidity is that described by Burri[2] in 1909, commonly known as "the India ink" method. A loopful of serum obtained from the lesion is mixed with a loopful of good India ink, preferably the Chin-Chin liquid pearl ink, and the mixture is rapidly spread over the slide as in making a blood-smear. After the film dries it is examined under an oil immersion lens, without mounting. The field appears as a brown or black background in which the treponemas, blood-cells, etc., stand out as colorless refractive bodies. Objection has been raised by Barach[3] to this method. He states that certain inks contain extraneous fibrils which resemble in form the treponema. I have never noticed this, but the fact that the presence or absence of the treponema must be determined not by finding the micro-organism but by seeing the unstained space which it occupied and that these spaces are often distorted in shape, appears to be a valid objection to this method.

The *Treponema pallidum* and the *Spirochæta refringens* can easily be differentiated by this method, but it is impossible to distinguish between the *Treponema*

2. Burri: Das Tuschererfahren als einfaches Mittel zur Lösung einiger schwierigen Fragen der Bakterioscopie, Jena, 1909.

3. Barach: Warning Against the India-Ink Method for the Spirochæta Pallida, THE JOURNAL A. M. A., Nov. 26, 1910, p. 1892.

*pallidum* and the *Treponema dentium*. This applies, however, only to smears taken from lesions of the mouth.

### SECTIONS

In making sections of syphilitic tissue there is no doubt that the Levaditi method (impregnation with nitrate of silver) is best in tissues from hereditary syphilis, and that the Levaditi and Manouélian method is preferable in all other syphilitic tissues.

### FRESH SPECIMENS

By far the best method of finding *Treponema pallidum* is in fresh preparations by means of the dark-field condenser. When using this method as well as when making smears, great care must be taken in obtaining the material. No antiseptic solutions should be used prior to the examination. In primary lesions the surface is first washed with normal salt solution, and anesthetized, if necessary, with novocain and epinephrin, locally. The entire indurated area is then picked up with a long-pointed hemostat and squeezed until the tissue becomes blanched. Then the surface is scraped until a clear serum exudes, and from this serum the slides or smears are made, diluting with normal salt solution if necessary.

Serum can be obtained from secondary syphilids by first applying a Bier cup and then proceeding as above.

In lesions of the mouth the surface is rubbed thoroughly with normal salt solution and curetted, the upper surface being entirely removed before making the slides for examination.

Although I have attempted it frequently, I have never been able to demonstrate the presence of treponemas in the blood either in fresh specimens or smears. The advantages of the dark-field method are its quickness and its reliability. In a number of instances the treponemas have been demonstrated in the dark field in large numbers, while smears from the same lesion stained with

Giemsa and India ink show but a few or none present. The advantage of an early diagnosis is shown by the following cases:

CASE 1.—*Patient.*—Mr. M., Dec. 30, 1910. Clinically, a typical chancre of penis of three weeks' duration; glands palpable in both groins; no *Treponemata pallida* found by dark field or smears. Wassermann negative. Frequent examination revealed no *Treponemeta pallida.*

*Jan. 18, 1911.*—Without treatment, the primary sore almost entirely disappeared, the inguinal glands became smaller. A Wassermann reaction was negative. Up to the present time absolutely no clinical signs have manifested themselves. The patient at no time had any anti-syphilitic treatment, nor was the sore treated in any way except with boric acid.

CASE 2.—*Patient.*—Mr. R., Feb. 13, 1911: There was a slight indurated sore in the sulcus; the glands on the right side were enlarged and tender; examination under dark field showed many treponemas present.

*Feb. 14, 1911.*—0.5 gm. salvarsan administered intravenously.

*Feb. 15, 1911.*—No *Treponemata pallida* were found under the dark field.

Up to the present time no further clinical signs have manifested themselves. The Wassermann reaction was negative before the administration of salvarsan, positive ten days after the injection, negative twenty-four days after the injection, and has remained negative ever since.

CASE 3.—*Patient.*—Mr. A., April 18, 1911: The patient had a chancre of eight days' duration. Many *Treponemata pallida* were found in the dark field. On the same day the chancre was excised and 0.5 gm. salvarsan given intravenously. Up to the present time, no secondary rash or other manifestations have developed. A Wassermann reaction was positive before the administration of salvarsan and weakly positive ever since.

### SERUM DIAGNOSIS

The diagnosis of syphilis by the above-mentioned methods is naturally confined to the early stages of the disease. By means of the Bordet-Gengou[4] complement fixation reaction, as described first in this connection by Wassermann, Neisser and Bruck,[5] another method of

4. Bordet-Gengou: Ann. de l'Inst. Pasteur, 1901, p. 289.
5. Wassermann, Neisser and Bruck: Deutsch. med. Wchnschr., 1906, xxxii, 745.

laboratory diagnosis has been added to the physician's armamentarium. The consensus of opinion at the present time is that this reaction in syphilis is a specific antigen-antibody combination in which the antigen used is closely related to the lipoid substances, and in which the antibodies react not alone with the specific syphilitic antigen but also with some of the constituents of normal tissue. It is probable that the substances which owe their origin to the luetic infection possess a certain chemical relationship to lecithin.

On account of the complicated technic of this reaction many investigators have attempted to modify and simplify it. The Noguchi[6] method is best known in this country and appears to be of sufficient value to be used instead of the method described by Wassermann. It also eliminates one source of error by the use of an antihuman amboceptor and furthermore requires a smaller amount of blood-serum. This becomes quite a factor when endeavoring to obtain a sufficient amount from infants. In a long series of cases in which both the Noguchi and the Wassermann systems have been used the results were parallel when the same antigen was employed.

In obtaining blood for these reactions a tourniquet is applied to the arm and one of the superficial veins of the forearm is punctured with a dry sterile needle. About 5 c.c of the blood are permitted to flow into a clean test-tube and allowed to coagulate in the position of an agar slant. The tube is then turned over and the clear serum separated from the clot without the need of a centrifuge. In children, and in people with small superficial veins, the blood is collected from the finger in a Wright's tube. Care must be taken that in collecting the patient's blood no alkaline or acid liquids come in contact therewith. The serum should be kept on ice until ready to use, a badly infected serum may give erroneous results. If an

6. Noguchi: Jour. Exper. Med., 1909, xi, 392; Serum Diagnosis of Syphilis, Ed. 2., 1911.

acetone-insoluble antigen is used, the serum can be employed in both an active or inactive state.

The antigen used in the laboratory, in both the Wassermann and the Noguchi systems, is made from syphilitic or normal human heart and liver extracted with alcohol, fractionated with acetone, and then dissolved in methyl alcohol. It is titrated by the method described by Noguchi. An antigen can be obtained from either syphilitic or normal tissue, but from my experience it appears that the percentage of good antigens obtained is greater when syphilitic material is used. It must be remembered that the reaction is a quantitative one and an exact proportion must be maintained between the various reagents. Great care is necessary in selecting a proper antigen and the variation in results reported by different workers is frequently due to the use of an improperly made and titrated antigen.

For those working continuously with the complement fixation reaction, there appears to be no advantage in the use of antigen and amboceptor dried on filter paper. Experiments with these papers, when controlled with liquid reagents, have shown that those papers impregnated with antigen will not keep as long as a liquid extract maintained in the ice-box.

### DIAGNOSTIC VALUE

Reports of the diagnostic value of the complement fixation reaction varies greatly with different workers. In a series of 1,350 cases my results have been as follows:

| | Percentage + |
|---|---|
| Primary syphilis | 93 |
| Secondary syphilis | 97 |
| Tertiary syphilis | 82 |
| Hereditary syphilis | 100 |
| Early latent syphilis (Treated and untreated) | 56 |
| Late latent syphilis (Treated and untreated) | 60 |
| Tabes | 77 |
| General paresis | 98 |
| Cerebrospinal syphilis | 71 |

In a total of 142 cases, from which syphilis could not be excluded as an etiologic factor, the number of positive cases was 106; negative, thirty-six.

In cases from which syphilis can be eliminated as a factor: Total 182: Positive, seven; negative, 175.

Of the positive, six were leprosy and one carcinoma. The presence of hereditary or acquired lues could not be excluded in three of these cases.

The great value of this reaction in the detection of syphilis as an etiologic factor and of latent syphilis has been amply brought out by many investigators. Chronic myocarditis, and aortitis, valvular insufficiency, aneurysm, hemiplegia, adult epilepsy, cirrhosis of the liver, may now be traced to a syphilitic etiology.

In my series there are a number of syphilitic families in which positive reactions were obtained in some of the offspring showing no clinical symptoms.

The reaction is also of great value in the determination of the need of further treatment. Most all observers have found that positive results are more frequent in untreated or insufficiently treated patients.

### EFFECT OF TREATMENT

From the literature, and also in my experience, in the majority of cases a positive reaction becomes negative after the administration of a greater or less amount of mercury. In hereditary lues a positive reaction may persist despite the administration of a large amount of mercury and potassium iodid. It may persist after the disappearance of the clinical signs, or it may return after once having become negative, the administration of mercury having been stopped. In a series of 116 cases, in which salvarsan has been administered, the results were as follows:

Twenty-eight patients were given more than one dose; three were given more than two doses. All were positive before administering the salvarsan.

| | Per cent. + |
|---|---|
| End of two weeks | 51 |
| End of one month | 37 |
| End of two months | 18 |
| End of three months | 16 |
| End of four months | 15 |
| Remained positive to date | 18 |

Returned after once negative, 11 per cent.

CEREBROSPINAL FLUID

The usual methods of examining cerebrospinal fluid for the purpose of determining the presence or absence of syphilis are, cytologic examination, the Nonne[7] ammonium sulphate reaction, the Noguchi[8] butyric acid reaction and the complement fixation reaction. In the main, these reactions have their greatest value in patients suspected of having tabes, cerebrospinal lues, general paresis, and in psychiatric cases. In using the Nonne reaction I use the ring method of Ross and Jones.[9] In the butyric acid test care must be taken that the butyric acid is fresh and that only a flocculent precipitate, which appears within two hours after heating, is called positive. In carrying out the complement fixation reaction with the cerebrospinal fluid, it has been found by titration that an amount equal to ten times the quantity of blood-serum must be used. The presence of a positive Nonne and butyric acid test indicates an increase in the globulin content of the cerebrospinal fluid, and may be obtained in cases of acute inflammatory meningitis. In tabes I have obtained positive reactions in the cerebrospinal fluid, while the reaction on the blood-serum was negative. This result has also been obtained in several cases of cerebral syphilis.

In a few cases of tabes the globulin content did not appear to have been increased, but the complement fixation reaction was positive. In none of these cases, however, was the cell-count positive. In general paresis the inhibition of hemolysis is almost always absolute.

7. Nonne: Clinical Diagnosis of the Syphilogenous Diseases of the Central Nervous System, July 24, 1909, p. 289.
8. Noguchi: Proc. Soc. Exp. Biol. and Med., 1909, vi, 77.
9. Ross and Jones: Brit. Med. Jour., 1909, i, 1111.

In tabes, cerebrospinal lues and general paresis the complement fixation reaction should be done both on the blood-serum and on the cerebrospinal fluid, for the syphilitic etiology in some cases may be missed if the blood-serum alone is examined.

The complement fixation reaction with relation to milk, urine, transudates, etc., will not be entered into as they have no practical bearing on this subject.

A large number of modifications of the original Wassermann reaction have been described, but so far, with the exception of the Wassermann and Noguchi systems, all are subject to the same criticism, namely, that indefinite amounts of the amboceptor, complement, and blood-corpuscles are used.

The various precipitate reactions described are not as reliable as the complement fixation reaction.

### MEIOSTAGMIN REACTION

Ascoli and Izar[10] utilize the fact that when a specific antigen and a serum containing its corresponding antibody are mixed a lowering of the surface tension of a drop results. This phenomenon has been utilized in the diagnosis of syphilis by first determining the number of drops in a given bulk of patient's serum, and then determining the variation from that number after the antigen has been added to a like quantity. My experience with the stalagmometer of Traube leads to the conclusion that this instrument is too delicate for the use of the general practitioner. The surface tension is changed by so many factors, such as vibration, temperature, specific gravity, etc., making it of little use outside of a well-equipped physical laboratory.

### SCHURMANN COLOR REACTION

With a limited number of serums I have been unable to obtain results as noted by Schurmann. A number of definitely negative serums gave a positive reaction.

10. Ascoli and Izar: München. med. Wchnschr., Jan. 11, 1910, p. 62; Jan. 25, 1910, p. 182; Feb. 22, 1910, p. 403; May 3, 1910, p. 954; May 31, 1910, p. 1170.

## CONCLUSIONS

1. Examination by the dark-field condenser is the surest and most rapid method of determining the presence or absence of the *Treponema pallidum*.

2. The success with fresh specimens and smears depends largely on the care used and the manner of making the preparations to be examined.

3. The early diagnosis of syphilis becomes more important on account of the advantage obtained in aborting the disease in many instances by the use of salvarsan.

4. Serum diagnosis of syphilis is of great value throughout the course of the disease after the infection becomes systemic.

5. The complement fixation reaction is of value in determining a syphilitic etiology and the effect of treatment.

6. In patients under treatment a negative complement fixation reaction is not of the same value as a positive one in determining the presence or absence of the disease.

7. In certain forms of parasyphilis a negative reaction does not entirely exclude the presence of syphilis.

8. In syphilis of the central nervous system the complement fixation reaction should be done with the cerebrospinal fluid as well as with the blood-serum.

9. Great care should be taken in selecting and making antigens used in the complement fixation reactions. The reaction is a quantitative one and the accuracy of results are dependent entirely on the quantitative relation between the various reagents.

10. With properly selected antigens the Wassermann and Noguchi methods are equally reliable.

# VISCERAL SYPHILIS

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CHICAGO

Visceral syphilis is not limited to the tertiary stage. Lesions of the viscera may occur during the secondary period of syphilis, but visceral syphilis occurs chiefly in the tertiary period.

Clinical evidence of visceral syphilis occurs more frequently in disease of the liver or heart and blood-vessels than of any other organs of the body. Fever of a septic remittent or intermittent type is not an infrequent event. It is not unusual to find chills, fever and sweat resembling malarial fever. Indeed, the fever of visceral syphilis is frequently mistaken for malaria, tuberculosis, typhoid fever or rheumatism. The fever will frequently recur at intervals over years of time. Gummas are usually the source of such fevers and the fact that a gumma may spontaneously heal and disappear, and, especially if the patient is put to rest, is not usually recognized. While the condition may be obscure in these febrile conditions, a thorough examination, including a close survey of the liver and other organs of the body, the serum Wassermann test and the use of mercury and the iodids will frequently clear up the diagnosis.

Syphilis of the respiratory system is not of common occurrence. The trachea, the bronchi and the lung may be involved. A congenital syphilis of the lung in the form of a white pneumonia, described by Virchow, is not of frequent occurrence. Those whose practice is limited to the diseases of children frequently recognize the disease. Usually it is fatal. Acquired syphilitic

infection of the trachea, bronchi and the lung is of such infrequent occurrence that it does not come within the experience of the general practitioner and is seen only as a rare event in a rather large hospital practice. Gummas resulting in ulcer or in scars and contraction of the trachea and bronchi are sometimes found and recognized by concurrent evidence of syphilis elsewhere in the body, or by the improvement from the use of antisyphilitic treatment. The symptoms are not at all characteristic, usually consisting of cough and dyspnea with an expectoration free of tubercle bacilli and evidences of other diseases. Acquired syphilis of the lung usually occurs in the form of gummas near the hilum or sometime within a lobe. Cough with chills and an intermittent type of fever, rather profuse expectoration with enlargement of the superficial lymph-glands as well as those of the mediastinum are usually found. The physical examination may simulate that in tuberculosis or in bronchiectasis. The absence of tubercle bacilli in the sputa, the evidence of syphilis through the history of the patient or evidence of syphilis elsewhere and response to antisyphilitic treatment help to verify a diagnosis.

CASE 1.—*Patient.*—I have seen one patient of this kind: H. S., aged 26, Hebrew, single, traveling salesman, presented himself with a complaint of cough, febrile condition, sweats at night, loss of weight and strength, diminished appetite. At first he denied syphilitic taint. Expectoration was rather profuse and contained mucopus, saprophytic bacteria and no tubercle bacilli.

*Examination.*—There was a relative dulness over the left upper lung, especially in the region of the interlobular fissure behind, increase of tactile fremitus and voice sounds, bronchovesicular breathing and moist râles, both fine and coarse. Lymph-nodes existed in the posterior triangles of the neck, the supratrochlears and other superficial glands enlarged and firm.

The patient was closely questioned because of the presence of the enlarged lymph-nodes of the postcervical region and of the supratrochlear region. Finally, he admitted an acquired syphilis of five years before with only superficial and inadequate treatment.

*Treatment and Result.*—**The use of inunctions of mercury and a moderate dosage of iodids resulted in surprisingly rapid improvement and a final disappearance of all evidence of local lesion and of symptoms. The patient continued on the treatment for a year and remained well.**

A chronic bronchopneumonia is said to occur in the lung of a syphilitic type, but the literature does not contain many examples and I have never seen one that I have recognized.

Tertiary syphilis of the alimentary canal is recognized but is rare. Ulcers of the esophagus following a probable gumma, or by extension from ulcerative processes of the pharynx, occur with resulting difficulties in swallowing or the formation of strictures from the scar contraction.

Diffuse acute gastritis is said to occur and also syphilitic ulcer. Nodular gummata of the stomach are rare, but cases are cited, including descriptions of this condition by Simon Flexner.

Enteritis with swelling of the lymph follicles and enlargements of the mesenteric glands occurs rarely. Ulcers may result from follicular enteritis. Gummata may appear in the mucous membrane of the intestine with resulting ulcer and, if healed, with scar contraction and stricture.

The rectum may be infected directly from the vulva or from condylomata. Ulcers of the rectum of syphilitic origin are more common in women than in men.

The spleen may be enlarged in the early stage of syphilis. Gummas of the spleen are common and one of the sources of fever. Cicatrices of healed gummas are frequently found post mortem. Amyloid degeneration of the spleen of syphilitic origin is seen in patients with syphilitic amyloid liver.

The liver is the most common seat of visceral syphilis. The syphilitic process may consist of a diffuse interstitial hepatitis with enlargement of the organ, which may occur congenitally. In this condition the

liver is large, smooth and the cut surface is of a gray yellow appearance. It may appear early and usually is fatal. The same type may occur in later life, most commonly in adolescence associated with other evidences of syphilis in the form of interstitial keratitis, rhagades, Hutchinson's teeth and sometimes with small stature amounting to infantilism.

A diffuse interstitial hepatitis of the acquired type may occur, which partakes frequently of hypertrophic cirrhosis. In this type the liver is enlarged, smooth and sometimes tender to the touch. There may be a moderate jaundice, and fever of the intermittent type is not infrequent associated with chills and sweats. An atrophic cirrhosis with recurring ascites may also occur in acquired syphilis. This may be a later stage of the hypertrophic form. Gummas may appear in the hilum of the organ and by pressure on the portal vessels produce ascites.

The lesion may consist of gummas in the form of tumors measuring from 2 mm. in diameter to the size of a fetal head. They may be single or multiple. These tumor masses may produce enormous enlargement of the organ. There may be jaundice. Usually there is an intermittent or remittent type of temperature with or without chills, and frequently there are night sweats. There may be great tenderness and spontaneous pain. With small gummas the clinical phenomena may last for a variable period and disappear. Recurrences over years of time are not unusual. Lessened strength, endurance and loss of weight and a muddy complexion are of frequent occurrence. Gummas situated near the blood-vessels or gall-bladder may simulate other diseases. The following case is an example:

CASE 2.—*Patient.*—L. S. S., aged 37, railway engineer, contracted lues in 1897. In June, 1898, he noticed dull pain in the border of ribs in the region of gall-bladder. This was aggravated by motion. Sometimes after meals he experienced severe attacks of colicky pain radiating from the right hypochondrium. He had also suffered from chill, fever, sweat and

jaundice. There was some nausea with these attacks. The paroxysms of chill, fever, sweat and pain occurred at irregular intervals during 1898 and then there was a period of relatively good health.

*Examination.*—On Sept. 29, 1899, the patient was first examined. His weight was 145 pounds, a loss of 20 pounds. A slight coating of the tongue. No enlargement of lymph palpable glands. The lungs and heart presented no abnormal condition. The liver was moderately enlarged and easily felt below the costal edge. The border was smooth, rounded, slightly resistant, and very tender to the touch. A mass could be felt in the region of the gall-bladder. The urine (specific gravity 1.020) contained a trace of bile, no albumin, no sugar, no casts. The blood showed no plasmodia; 9,000 leukocytes per c.c.

*Operation and Result.*—A diagnosis of calculous cholecystitis was made and the patient was sent to Mercy Hospital where he was operated by Dr. Christian Fenger. Multiple gummas of the liver were found; the largest one situated just behind the gall-bladder, which was infected by the gumma. No gall-stones were present. The patient rapidly recovered from the operation and made a rapid improvement with the use of inunctions of mercury followed by potassium iodid. The absence of syphilitic lesions of the superficial glands, skin, etc., and the typical symptoms of gall-stones due to the infection of the gall-bladder from a gumma, led to a wrong diagnosis.

The following cases are examples of gummas of the liver existing for a long period of time and unrecognized:

CASE 3.—*Patient.*— M. E. C., aged 54, presented himself Sept. 2, 1907. He had suffered from malaria while living in the south in 1887. Otherwise had rugged health until two years ago. Then illness developed in the form of fever with a temperature of 101 or more at night, sometimes preceded by chill and in the night the fever disappeared with a sweat. The morning temperature was either normal or subnormal. Medical care did not benefit him. The following summer was spent in Canada at the seashore. During this time the fever disappeared to recur the next fall with purpura of the legs. During this period he took quinin for what was supposed to be malaria, although no plasmodia were found in the blood. Following the purpura, copper-colored pigment spots remained in the skin. The summer of 1906 he spent in Europe and for a part of the time at Vichy, France, where he was sent by a physician of Paris. There the condition improved without anything but general treatment. On the return voyage fever

developed, which confined him to his bed during September and October. Then he was up and about again with a return of fever in December, 1906. This relapse of December, 1906, disappeared after general treatment with quinin and rest during January and February, and the patient remained well until July, 1907. Again fever appeared and continued until Sept. 2, 1907, the date of the first examination; then he had fever usually of 101 or more every evening, a normal temperature in the morning and sometimes a chill preceding the temperature of afternoon and a sweat at times in the night. He had lost a great deal in weight, from 178 pounds (maximum) to 132. His appetite was poor, and he was troubled with a good deal of flatulence. The bowels were constipated; patient had had hemorrhoids for years which often bled. He had no disturbance of the urinary tract; denied venereal disease. He used whiskey largely, as much as fifteen drinks a day at times.

*Examination.*—Patient looked ill and sallow; there was no subcutaneous fat; the muscles were flabby. There were no lymph-gland enlargements. Lungs and heart were normal; spleen palpable at the end of deep inspiration. The liver was tender and enlarged, projecting 2 or 3 cm. below the costal edge; surface smooth excepting at one point where a nodule in the right lobe could be felt. The whole organ was tender to the touch. Stomach tympany extended to the umbilicus. Rectum congested and many hemorrhoidal tumors appeared with the use of the speculum. Urine: a specimen, clear, specific gravity 1.015, acid, a faint trace of albumin, a trace of bile pigment, no sugar, a few hyalin and faintly granular casts. The blood: hemoglobin 70 per cent. (Dare), reds 4,800,000, whites 9,000. No plasmodia were found in either fresh or stained specimens of the blood.

*Treatment and Result.*—In spite of the fact that the patient denied syphilis, a diagnosis of probable gumma with interstitial hepatitis of syphilitic origin was made and he was treated at the Presbyterian Hospital, Chicago, for about six weeks by the deep intramuscular injections of bichlorid of mercury in the dose of 1/6 to ⅓ gr. given every day or every other day. Following the use of 20 injections of mercury he was given gradually increasing doses of potassium iodid. Under this treatment there was a rapid subsidence of all symptoms and of the evidence of visceral disease. The improvement was phenomenal, the patient rapidly gaining in strength and weight and a full restoration to health. The patient has remained so until the present time. A recent communication from him includes the statement that his weight is the full normal and he is entirely well. Subsequent to his treatment in the Presbyterian Hospital his physician carried out similar treatment at periods during 1908 and 1909.

CASE 4.—*Patient.*—C. K., aged 60, married, railway business, presented himself on Dec. 24, 1904. He had contracted lues fifteen years previously. For ten years he has had disturbance of the stomach in the form of pain in the epigastrium, of a cramping character which came on soon after taking food. The pain sometimes is relieved by an aromatic drink. The pain is dull and sometimes griping in character. Recently he had used a stomach-tube which has diminished the attacks and usually immediately relieved him. No analyses have been made of the stomach condition. A year before examination he suffered from what was described as ulcer of the mucous membrane of the nose for which he received local treatment and was also given some potassium iodid. Recently, the pain in the epigastrium had recurred and was not relieved by lavage. There was an occasional chill with slight fever and sweat but these febrile attacks were not continuous.

*Examination.*—The patient's general appearance was healthy, and general nutrition good. There were no palpably enlarged lymph-glands. Throat was normal; lungs negative; the left heart border dulness extended to the left nipple. The apex-beat was normally situated, the heart action regular. The aortic second tone was accentuated. There was no palpable thickening of the blood-vessels. The arterial tension was 140. The liver was palpably enlarged, projecting 5 to 7 cm. below the costal edge. It was smooth, firm and tender to the touch. A distinct mass could be felt in the right lobe near the region of the gall-bladder. The spleen was not palpable. Stomach tympany extended to the umbilicus. Pupillary and patellar reflexes were normal. Temperature was 100.8, pulse 90, respiration normal. Blood: 3,800,000 reds, 60 per cent. hemoglobin (Dare), 17,400 leukocytes with polynuclears predominating. Urine: a specimen, 1.015, acid, trace of albumin, a few hyalin and finely granular casts. A twenty-four-hour urine amounted to 1,000 c.c., specific gravity 1.015. An Ewald meal showed a total acidity of 28, free hydrochloric acid 15, combined 13, no lactic acid, no blood, no increase of leukocytes.

*Treatment and Result.*—The patient was given deep intramuscular injections of salicylate of mercury in the dose of 1 grain every day or every second day and after twenty injections was given potassium iodid in the dose of 15 to 30 grains, three times a day. Immediate improvement followed the mercurial treatment with a rapid recovery to good health. The patient not only was restored to a good condition of health but all stomach symptoms disappeared and have remained absent to the present time. A recent Wassermann test was negative.

CASE 5.—*Patient.*—F. B. S., a German-American, 38 years of age, a clerk by occupation, presented himself on Jan. 5, 1905. He complained of great general weakness, poor appetite, heaviness and fulness in the stomach after meals, a sense of weight in the right hypochondrium with soreness, pain in the right side and a fever every day in the late afternoon with occasional sweats at night. He had contracted lues fourteen years previously and had taken treatment for it off and on for years.

*Examination.*—The patient was a man of good physique with poor general nutrition, a muddy complexion with slight yellowness of conjunctiva. The temperature was 100, the pulse 90, no palpable glandular enlargements. The mucous membranes were rather pale, the tongue moderately coated. The throat and lungs were normal. The heart presented no abnormal signs. The liver was distinctly enlarged, projecting 5 or 6 cm. below the costal edge, and was somewhat firm and tender. In the parasternal line there was a distinct mass in the right lobe. The spleen was not palpable. There was a spindle-shaped swelling of the right femur at the junction of the middle and lower thirds. It was nodular, tender and was painful when the patient attempted to walk. An *x*-ray examination of the thigh showed a swelling of the shaft of the bone which involved not only the periosteum but the bone itself. The blood examination showed 63 per cent. hemoglobin (Dare), 4,200,000 reds, 10,000 whites. The urine: 1.015, a trace of albumin and a few hyalin and granular casts.

*Treatment and Result.*—The patient was treated at the Presbyterian Hospital for three weeks. During this time he was given deep intramuscular injections of 1 grain of salicylate of mercury every day followed by potassium iodid in the dose of 10 to 30 grains three times a day. Immediate improvement followed the use of mercury and continued uninterruptedly until all evidence of disease disappeared and on April 27, three and a half months after he was first seen, he presented no physical evidence of disease and showed a gain in weight of 20 pounds. He has been under observation since then and has had a series of injections of mercury for two periods and the use of the iodid after the injections. He remains entirely well.

Many other cases could be cited, as this form of visceral syphilic is very common.

There can be no question that diffuse interstitial hepatitis of a chronic type is of rather frequent occurrence and when treated in a general way develops into a

cirrhotic atrophic type. Early antisyphilitic treatment would in many instances cure such patients. The scarred liver, the result of gummas, or the botryoid liver consisting of deep fissures comprised of dense bands of connective tissue partially or completely separating portions of the liver into small lobules, is usually without symptoms. Such a type of liver usually is a sequel of syphilis of the liver either congenital or acquired, or may be a latent manifestation.

### SYPHILIS OF THE KIDNEYS

Syphilitic nephritis is a recognized entity. It usually occurs in the secondary stage, but may develop later. Nephritis of this type is frequently aggravated by the use of both mercury and the iodids. The symptoms and urine condition are those of a chronic parenchymatous or sometimes of the interstitial type of nephritis. Frequently, one is obliged to cease the use of mercury or of the iodids because of the aggravation of the condition brought about by their use.

This is not surprising when one knows that mercury is excreted by the kidney and may be found in the urine as late as one year after the use of that drug, especially by the intramuscular injection method. Syphilitic nephritis may lead to an early death, may develop into a chronic type and continue as ordinary nephritis even when all syphilitic disease is apparently eliminated.

Amyloid kidney is of syphilitic origin, is of rare occurrence and gummas of the kidney are rare.

### SYPHILIS OF THE HEART AND BLOOD-VESSELS

The toxin of syphilis falls with unusual severity on the heart and blood-vessels. The morbid phenomenon occurs in the following forms:

1. In the form of nodular para-arteritis which may involve any of the small arteries of the body, but occurs most frequently in the arteries of the circle of Willis.

2. As an acute gummatous endarteritis of vessels of medium size and sometimes of large ones of the brain

and also of the aorta. This is the type in which perforation of the arterial wall may occur and when it involves the aorta results in sudden death.

Such a case I have had in a man 37 years of age, who suffered from syphilis eight years before. He had inadequate treatment because he would not submit to the necessary discipline and consequently suffered from frequent manifestations of syphilis, especially of the bones of the legs, head, etc. Without evidences of circulatory disease he suddenly developed dyspnea and in attempting to walk up a moderate-sized hill was seized with great pain in the precordium with a sense of suffocation and died within a few hours. Post-mortem revealed perforation of the aorta in the first portion of the arch and hemorrhage into the pericardium. The perforation was due to gummatous endarteritis.

3. Obliterative endarteritis involving small blood-vessels of the brain and elsewhere of the body, especially of the coronaries. This condition of the coronary arteries frequently results in fibrous myocarditis and development of heart inadequacy and with anginal attacks in the young, sudden deaths may supervene.

4. Syphilitic arteritis usually confined to the larger blood-vessels and especially to the root of the aorta and manifested by the easily recognizable changes in the intima and media. Gumma may occur in the heart-wall and interfere with the conductivity of the muscular fibers. It may appear in the bundle of His and cause heart-block.

### RELATION OF SYPHILIS OF BLOOD-VESSELS TO ANEURYSM

It has been estimated that from 20 to 80 per cent. of aneurysms are related to syphilitic disease of blood-vessels. This occurs because of the effect of the syphilitic toxin on the intima, frequently resulting in a splitting of that coat and an undermining of the wall of the blood-vessel in consequence. The general nutrition of the coat of the vessel is further diminished by a not

infrequent obliterative endarteritis of the vasa vasorum. A general syphilitic arteritis most frequently affects the root and arch of the aorta and consequently aneurysms are most frequent in that part of the circulatory apparatus. Aneurysm may appear long after the initial infection. In recent time the *Spirochæta pallida* has been found in late syphilitic lesions of the aorta and explains the progressive nature of such lesions and resulting aneurysm.

The heart itself may show lesions in the form of verrucose endocarditis. The aortic valves may be involved with resulting aortic insufficiency. Not infrequently in this condition the coronary vessels are involved with resulting myocarditis and anginal attacks.

Syphilis of the heart and of the blood-vessels may be modified by antisyphilitic treatment, but unfortunately the good results of such treatment on other organs is not so fully realized.

### DIAGNOSIS OF VISCERAL SYPHILIS

This may be difficult at times and especially diagnosis of the lesion of organs which are rarely involved. The more commonly involved organs, the heart, blood-vessels, liver, spleen and kidneys, present evidences of syphilitic disease which may be very obscure, and on the other hand may be easily recognized.

The presence of a septic temperature of a remittent or intermittent type, associated with chill, fever, sweat, occurring at irregular periods with intervals of latency manifested by improvement and apparent health, should arouse one's suspicions of syphilis. The condition may be mistaken for tuberculosis or malaria more frequently than any other febrile condition. The fact that so many people deny syphilis and that others are ignorant of the presence of the infection makes it a little more difficult. I think, however, that one should not consider such negative evidence. If a most careful examination fails to show positive evidence of syphilis, one may utilize the

Wassermann serum test and the mercury-iodid therapeutic test with satisfactory results as a rule. Careful blood examinations will exclude malaria, and the tuberculin test may be used in afebrile conditions with comparatively satisfactory results.

The prognosis of visceral syphilis will vary with the condition. A thoroughly carried out treatment in syphilis of the liver of the acquired form is usually very satisfactory. In disease of the kidney one may modify the condition, but the damage done to this important organ prevents entire recovery. Syphilis of the myocardium may be also benefited by mercury and the iodids; and gummas of the heart, if not destructive of some important part like the bundle of His, may be dissipated by medication. Syphilis of blood-vessels of all types may be improved by brisk mercurial and maximum iodid treatment, but one is never sure of the result until the medication has been tried. In aneurysm, progressive disease of the blood-vessels due to latent syphilis may be somewhat modified by specific treatment, but a damaged blood-vessel cannot be restored to its original condition.

### TREATMENT

Mercury remains the best specific medication in syphilis of all stages. It may be used by mouth, by inunction, by deep intramuscular injection or intravenously. The deep intramuscular injections offer a most satisfactory and easily controlled method of giving a maximum amount of the drug. I think that it is the consensus of opinion that the drug should be administered for periods of from fifteen to twenty-five injections, daily or every second or third day and repeated again after an interval of three or four months until the patient is cured. The iodids are of value to dissolve and throw out of the body the morbid material of syphilitic infection. The iodids are of special value in gummatous disease. The dose may be small and give satisfactory results in some instances, and in others it must be

maximum amounting sometimes to 300 or 400 grains in twenty-four hours. The drug should be administered at periods like the mercurial treatment. In my experience the best results are obtained by using the iodid in periods when the mercury is not used. Salivation is less likely to occur than when the two are used coincidently.

Salvarsan is undoubtedly of great value in early syphilis and in syphilis with gummatous infiltration and ulceration. The fact that it will aggravate the morbid condition of a heart, blood-vessel or a kidney disease prohibits its use in those conditions. The fact that the best results are obtained in maximum dose by the intravenous method makes its use limited because of difficulty of giving it excepting by those who have a proper technic. A maximum dose of salvarsan followed by mercury is of undoubted value.

Mercury and the iodids have long been used with great satisfaction and we may continue to use them with gratifying results. I doubt very much if salvarsan will give us any better results than the rational use of mercury and iodids. Exceptions may occur in which salvarsan may prove a better remedy. The discovery of salvarsan and its undoubted specific effect on the spirilla warrants the hope that other drugs may be found of even greater specific action in syphilis and other diseases caused by these organisms.

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# THE VALUE OF THE WASSERMANN REACTION AND OF SALVARSAN

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## *I. THE VALUE OF THE WASSERMANN REACTION, BY A. KEIDEL*

These observations are based on 378 cases examined by the Wassermann test at the Genito-Urinary Clinic of the Johns Hopkins Hospital. The technic of the test followed the original method of Wassermann, Neisser and Brück, except in the preparation of the antigen, which was made by the method devised by Noguchi from syphilitic livers and from normal beef hearts. The unit of volume was also reduced and a water bath used in place of the air incubator.

Fifty of the cases examined were definitely non-syphilitic, including cases of epithelioma, sarcoma, tuberculosis, Reynaud's disease, scabies, acne, drug-rashes, and about twenty other various affections. In every case the reaction was negative.

There were sixty-four cases of undoubted syphilis with secondary manifestations at the time the test was made and of these 91.4 per cent. gave a positive reaction. Somewhat over half of the cases in this group had received no treatment and were positive, all those with a negative reaction being treated cases.

Of twenty-one cases with undoubted tertiary manifestations 62 per cent. were positive—four cases being doubtful. In all but three cases courses of antisyphilitic treatment had been received.

In twenty-three cases with early primary lesions and demonstrable *Spirochætæ pallidæ* twelve, or 52.2 per cent., were positive and one case was doubtful.

As no diagnosis had been made in most of the cases coming for the serum examination I was interested to note in what percentage the test had been of aid in establishing the diagnosis. In order that this may be clearly appreciated I have divided all the cases into five groups, as follows:

1. Non-specific cases. As already stated these were fifty in number, with 100 per cent. negative reaction.

2. Cases in which there were lesions of a doubtful nature and a negative history for syphilis. Of the seventy-one cases in this group, seventeen, or 24 per cent., were positive and three, or 5 per cent., doubtful.

3. Cases in which there were lesions of a doubtful or suspicious nature and an indefinite history of syphilis. This group is made up of sixty-one cases, twenty-three of which, or 37.7 per cent., were positive and two cases doubtful.

4. Cases in which there was a definite history of syphilis but no lesions. Eighty-three cases, twenty-one of which, or 25 per cent., were positive and five doubtful.

5. Cases in which there were suspicious or manifest lesions and a definite history of syphilis. This is the largest group, with 113 cases, of which ninety-three, or 82.3 per cent., were positive and six doubtful.

TABLE 1.

RESULTS IN THE EXAMINATION OF SIXTY-ONE VENEREAL SORES

| Duration of sores in weeks | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Number of cases | 11 | 14 | 11 | 11 | 2 | 5 | 3 | 2 | 1 | 1 |
| Positives | 3 | 6 | 6 | 7 | 0 | 2 | 0 | 1 | 1 | 0 |
| Negatives | 8 | 8 | 5 | 4 | 2 | 3 | 3 | 1 | 0 | 1 |

It was also of interest to note in how many cases in which the patients had venereal sores, a positive diagnosis of chancres could be made with the Wassermann test, in the absence of all secondary manifestations. Accordingly sixty-one patients with sores of from two days to

ten weeks' duration were examined and the results tabulated.

This table shows a steady increase in the number of positives from about 27 per cent. in the first week to about 64 per cent. in the fourth week, after which the number of cases rapidly falls off and the results are irregular. The importance of being able to recognize so large a number of chancres in the first week and practically all of them in the fourth week is obvious, but the table also shows that of the small number of venereal sores seen after the fourth week and unaccompanied by secondary manifestations such as a general glandular enlargement, over 25 per cent. may be chancres and can be diagnosed as such by this test.

Notwithstanding the fact that many of these patients had non-specific lesions, 42.3 per cent. gave a positive Wassermann. Of thirty-three cases in which the spirochetes had not been demonstrated, thirteen were positive. One patient had a positive Wassermann when first seen, four days after the appearance of the sore. An attempt was made to follow these cases in order to ascertain how many of them with the negative reaction subsequently developed secondaries. This was attended with small success, however, only six patients returning for observation, and all with secondary manifestations. Of these, three patients had been examined in the first week of the primary stage, two in the second week and one in the fourth week. In this last case the lesion had been treated with calomel powder from the outset.

In conclusion it need hardly be stated that a positive Wassermann test is for practical purposes conclusive evidence of syphilis. It is of scientific interest that the test may be positive in some non-syphilitic conditions such as leprosy, yaws, scarlet fever, and trypanosomiasis, tuberculosis, carcinoma and profound anemias, in none of which the diagnosis can be confused with syphilis, except perhaps in yaws. The only difficulty lies in the correct interpretation of the negative results. This, I am

convinced, may be met by careful attention to the technic of the test; by the use of only the highest-powered preparations, skilfully made and accurately titrated and by thorough familiarity with each step undertaken. The amount of treatment the patient has received and the time elapsed since the last treatment was discontinued should be taken into consideration. When the result is in doubt one should not hesitate to make repeated examinations at convenient intervals. With these precautions, I regard a negative Wassermann reaction while not of equal value with a positive result, almost as reliable.

### *II. THE VALUE OF SALVARSAN, BY J. T. GERAGHTY AND A. KEIDEL*

This report is based on a series of seventy cases which came under our observation and care in the Genito-Urinary Clinic of the Johns Hopkins Hospital, and in private practice.

#### TECHNIC OF THE ADMINISTRATION

Except in the first four cases, all injections were made intravenously into the median basilic, the median cephalic, or one or other of the superficial ulnar and radial veins. The needle was thrust directly through the skin into the vein in almost all cases. Even where the vein was not plainly visible it could readily be made so by the application of a tourniquet, and venesection was necessary in only a few cases on account of excessive subcutaneous fat.

The salvarsan was dissolved in about 100 c.c. of sterile salt solution in a sterile glass-stoppered bottle, and made alkaline with from 1.2 c.c. to 1.3 c.c. of 4-normal sodium hydrate solution, and enough salt solution added to bring the volume up to 240 c.c. so that each 40 c.c. of this solution contained 0.1 gm. of salvarsan. A glass-barrelled, 20 c.c. syringe provided with a two-way stop-cock and connections of small rubber

tubing was used, and the injection preceded and followed by a small quantity of salt solution.

Following the injections the patients were kept in bed in the hospital for two days, and then were allowed to resume their ordinary daily pursuits. As far as possible, all patients have been kept under observation and frequent Wassermann tests made, in order that failures and recurrences might be recognized as early as possible, and further treatment promptly instituted.

In the four patients treated intramuscularly the reaction to the drug was marked by most intense pain at the site of the injection, accompanied by the usual nausea, vomiting and headache. Following the intravenous administrations, in some instances, there was a slight rise in temperature, but this lasted for only a few hours and never exceeded 102 F. Owing to the pain, the intramuscular method was early abandoned in favor of the intravenous route, which was unaccompanied by local reaction, and did not incur the liability to abscess formation and painful indolent sloughs.

### RESULTS

Of the seventy patients treated those in the primary stage, with chancres of from one to three weeks' duration gave the best results. Only one dose was given in each case, and the sore healed promptly. The results to date in this class of cases have been particularly gratifying, inasmuch as no further manifestations of the disease have appeared, although periods of from two to five months have elapsed since the treatment.

Another group of cases in which the results seem to be very satisfactory is that in which the patients have received the drug following a vigorous course of mercury for periods of from a few months to a year, with the disease under control at the time. None of the cases in this group have so far recurred clinically, and in all that we have been able to follow serologically, the Wassermann reaction has remained negative. Some of

the cases have been under observation now for six months.

Cases with active secondary or florid syphilis, however, although all of the lesions and clinical manifestations have promptly disappeared following the treatment, and in many cases the Wassermann has become negative, almost invariably recur at some later date.

In cases with the late recurring secondary and tertiary lesions, or in which more or less diffuse syphilitic processes are present in the body, an absolute eradication of the disease with one or more doses of the drug can scarcely be expected. In none of our cases of this type have we been able to accomplish permanent results with salvarsan alone, although a marked beneficial effect on the lesions has almost always been observed.

In one case of congenital syphilis, with severe double keratitis in a girl 12 years old, no benefit resulted from an intramuscular injection of 0.2 gm. of salvarsan. In one tabetic receiving 0.5 gm. of salvarsan the painful crises disappeared and remarkable improvement in the general condition followed.

In six cases which were followed in order to observe the effect on the *Spirochætæ pallidæ* in open lesions, the organisms were seen to disappear in from five to twelve hours.

### COMPLICATIONS

In no cases have any untoward effects been observed directly attributable to salvarsan, with possibly one exception. In this patient ten weeks after the injection a palsy of the iris and accommodation in the right eye developed. The patient has been under treatment with potassium iodid, but the lesion is still present. A sufficient interval has not yet elapsed to make clear whether the palsy was syphilitic or caused by the salvarsan. In another case two months after injection, a paralysis of the external rectus of the right eye, such as is often seen in syphilis, was noted. The Wassermann reaction never became negative. The paralysis disappeared gradually

under treatment with mercury and potassium iodid, so that it seems fair to assume that it was syphilitic in nature. No ear disturbances have been observed.

### CONCLUSIONS

From our experience with this drug, we are convinced that it is an important addition to the therapeutics of syphilis. In almost every case in which visible lesions were present complete disappearance followed the injection and marked improvement in the general condition of the patient was a constant feature. In all cases refractory to mercury, the response to salvarsan has been prompt and striking. The drug is indispensable for the treatment of patients who do not tolerate mercury. A study of our statistics does not warrant us in expecting a complete cure of syphilis and absolute immunity from recurrences in the majority of cases after the use of only one or two injections. A small number of cases which have been followed by us for four or five months without recurrences justifies the belief that one injection of salvarsan will effect a complete cure in some cases. Salvarsan is without doubt of equal value with a long course of mercury and potassium iodid in the cure of lesions. It has, however, the very great advantage of simplicity of administration, and causes the lesions to disappear with great rapidity. Moreover, it saves the patient from the damage done by the luetic toxin during the period necessary for the control of the disease by means of mercury.

We want particularly to emphasize the fact that the use of salvarsan has now passed beyond the experimental stage. One should no longer make it his object to see how much good can be done with one or more injections of this drug, but rather of how much value it can be made to assume in the treatment of syphilis when combined with other drugs.

The superior ability of salvarsan over mercury to kill rapidly the *Spirochætæ pallidæ* in the tissues has been

demonstrated beyond question, and salvarsan is therefore indicated in every case of syphilis, when not specially contra-indicated, even in those cases in which it seems advisable to supplement it with the subsequent use of mercury.

From our experience at present, we strongly advocate a vigorous course of mercury following the injection of salvarsan, continued for about six months and possibly then followed by another dose of salvarsan. In the primary cases, and those already well under control with mercury, it seems fairly probable that salvarsan may be sufficient to eradicate the disease.

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# THE DISADVANTAGES INCIDENT TO THE ADMINISTRATION OF SALVARSAN

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Salvarsan in its present form can never become a popular remedy. Paul Ehrlich, however, is so ingenious that any day he may invent a modification that will be more easily administered, and will be even less toxic.

There are three determinations of salvarsan that are of fundamental importance; its poisonous action on the *Spirochæta pallida;* its selective action on epithelial tissue; and its selective action on the tissue of nerves. Its stimulating action on epithelial tissue is shown in the marvelous way mucous patches and luetic ulcers epidermize under its influence. Its selective action on nerve tissue, however, is what immediately interests us in this paper.

On the introduction of salvarsan, the attention of observers was fixed on the optic nerve, as it was feared that salvarsan might, like atoxyl, cause amaurosis. But experience accumulated, and as no reports of disagreeable ocular symptoms were at first recorded it was hoped that at last an arsenic preparation had been discovered which had no attendant grave toxic disadvantage. Still later experience tends to show, however, that salvarsan is not entirely free from poisonous influences on the nerves in the orbit. Finger was among the first to draw attention to these, but the instances reported are not so typical as those from atoxyl and arsacetin. They have been observed very infrequently, and it seems often to be a question whether they are owing to syphilis, to salvarsan, to a previous treatment with atoxyl, or to

some other cause. It must be remembered that the hope and the interest aroused by the new drug have induced thousands of old syphilitics to apply for treatment for all sorts of chronic ailments not necessarily caused by syphilis at all, and that among these old ambulatory pathologic museums there would necessarily be a great number suffering from ocular disabilities.

But while attention was fixed on the eye, the ear seems to have suffered, as since the introduction of salvarsan an unusual number of troubles with the vestibular apparatus have been observed in early syphilis. It would seem that the arsenic in salvarsan acts true to kind and that we cannot entirely escape the predilection of this metal for nervous tissue. Implications of other nerves have also been reported, but, of course, of infinitely less consequential gravity. In any fair consideration of the detrimental effect of salvarsan on the nerves, however, we must always take into account the patients with whom we are dealing. Besides having syphilis, which itself attacks the nerves, they, as a class, habitually over-indulge in drugs that are strongly neurotropic, such as alcohol, tobacco, coffee and tea, and in addition put their nervous systems to the hardest kind of use, such as exposing the eye night after night to strong electric lights.

It is most interesting to consider for a few moments the selective action of arsenic on the nervous system. Arsenic has been used by therapeutists for ages as a nerve tonic, and although this experience has not the definiteness of a laboratory experiment, it, nevertheless, has value as indicating this metal's neurotropic nature. Accumulated clinical impressions always have a value. Furthermore, the marvelous action of salvarsan as a tonic is common to it and to the other arsenic preparations, and is probably due to its combined stimulating effect on epithelial and nerve tissue. The frequent occurrence of herpes zoster in those who are taking arsenic is another expression of the stimulating effect

of this drug on the nerves. Then we have the selective action of atoxyl and arsacetin on the optic nerve, causing amaurosis. Furthermore, dentists constantly use arsenic to kill nerves. Arsenic has also been used for ages as a topical necrotizing agent in the treatment of epithelioma, and those who so employ it almost invariably come to the conclusion that the metal exerts a selective action on the diseased epithelial cells. At the same time, the atrocious pain that it causes when used on epitheliomas impels to the belief that the nerves at the same time are receiving special attention. The intolerable pain sometimes felt when salvarsan is employed, either subcutaneously or intramuscularly, is easily recognized by the experienced as the same kind of pain complained of by patients when arsenic is used topically in epithelioma.

Therefore, we recognize the neurotropic action of arsenic as a nerve tonic, as a herpetogen, as an amaurotic, as a nervocide and as a dolorific. Accordingly, it follows that when an unusual number of vestibular affections are reported in early constitutional syphilis, and therefore at a time of life, as well as at a stage of the disease, when such affections are rare, there naturally arises a grave suspicion that salvarsan may be the cause.

But the surprise lies in the fact that it is so little toxic. It is long since anything so dramatic as the introduction of salvarsan has occurred in the practice of medicine. The metal forming its main ingredient has played a romantic part in the world's history as a poison. Ehrlich, by combining this metal with other elements, changed at will its mode of action as regards this or that kind of animated protoplasm, so that it became almost indifferent even to its beloved nerve-cells and yet retained a strong affinity for the cells that constitute the virus of syphilis.

At present very few men rely solely on salvarsan in the treatment of syphilis. It is now used in conjunction with the two other great specifics, mercury and iodid of potash. On informing a patient that salvarsan is not

an absolute specific for syphilis, clearing up the disease and all its manifestations at one stroke, it is interesting to watch the mental reaction that takes place. The patient almost invariably concludes that the remedy is worthless. Yet a medical man, for the sake of his own reputation, must tell the facts of the case. Furthermore, it is dangerous to tell a patient that he is cured, for then he is thrown off his guard in case further manifestations of his disease should appear.

Another feature tending to diminish the popularity of this remedy is the difficulty surrounding its administration. It cannot be taken by the mouth, and if given either intravenously, intramuscularly or subcutaneously, it has to be prepared with minute care, and the injection has to be carried out under the strictest antisepsis, as the drug itself is an irritant, but not an antiseptic.

Many drugs such as morphin and cocain are so bland in their action on the tissues that we never expect any local trouble to follow their hypodermic use. Others, while irritant and harmful, are at the same time antiseptic, and therefore the injured or necrosed tissues are not exposed to the additional danger of sepsis. One of the great points in favor of the administration of salicylate of mercury intramuscularly is that this particular preparation is slightly soluble and a good antiseptic, and yet so slowly soluble as to act almost as powerfully as an insoluble mercurial salt. Among the drugs used subcutaneously or intramuscularly, salvarsan is distinguished by its injurious action on the tissues, and often gives rise to local necrosis. K. Martius found that it did so in every case he investigated. Once, where the injection was thrown into the gluteal muscles, there was no tendency to heal, although three months had elapsed. In two instances the necrotic mass had to be excised.[1] Salvarsan, however, although it acts so injuriously, is not an antiseptic, and therefore if the technic is not

1. Martius, K.: Local Action of Salvarsan at Point of Injection, München. med. Wchnschr., Dec. 29, 1910; abstr. in THE JOURNAL A. M. A., Feb. 4, 1911, p. 388.

perfect and germs happen to be included in the injection, they have an excellent opportunity to develop in the injured or helpless tissues. Septic infection, sometimes fatal, may therefore be a consequence of the administration of this remedy.

When salvarsan causes an arsenic necrosis that involves the whole skin, an ulcer results that is very slow in healing, and there is no telling when such an ulcer may develop. I have seen a patient get a necrotic ulcer from an injection of salvarsan who, several weeks before, had received an injection that passed off without any more than the ordinary inconveniences.

Then again, when salvarsan is given either subcutaneously or intramuscularly, the drug may not be absorbed. Schreiber had a patient, a doctor, who became so tired of the annoying deposit of salvarsan as to beg to have it cut out, and over 80 per cent. of the drug was removed from the local deposit. I have seen a number of these deposits, and the percentage of their occurrence must be quite high. In many instances they lie almost inert in the tissues causing pain only when pressed on, while in other cases they are very annoying. When the deposits are very annoying, the patient may ask to have the sac emptied, and the affair ends. When such a deposit is inert it is a question what to do with it; whether to leave it alone or to advise its removal. If left alone it might possibly give rise to arsenic poisoning by slow absorption, although I have never seen it do so. When the remedy lies unabsorbed, it, of course, does not act as an antisyphilitic, and may, if solely relied on to combat a progressive, destructive gumma, occasion serious loss of time. In other words, it constitutes a delay in treatment, possibly at a critical moment.

The intravenous method is undoubtedly to be preferred, as when the patient receives the dose, he has it then and there in sufficient quantity, and with little fear of any local trouble. But this way of administering salvarsan constitutes a surgical operation, demanding

skill, intelligent care, and the strictest antisepsis, and more care and time indeed are here necessary than in many more pretentious operations. Above all things, an absolutely perfect solution must be obtained, as the injection of solid particles into the venous circulation is not permissible. So important is it to get a faultless solution that Schreiber always kept this step under his direct supervision. I never saw him give the actual injection into the vein, but I never saw an injection given in his clinic wherein he did not supervise the dissolving of the salvarsan. The greatest care is also necessary to keep adventitious particles out of the fluid. Sterilized distilled water should be used in making the solution, and no cotton should be employed in stoppering the bottles or in wiping the instruments lest cotton threads get into the fluid. The solution injected into the veins should not be a concentrated one, as it is an axiom that even harmless salts, when employed intravenously, should be well diluted. Furthermore, if by accident some of the salvarsan solution should escape into the subcutaneous tissues, it irritates far less when highly diluted than when concentrated. A concentrated deposit of salvarsan at the bend of the elbow where it may annoy for weeks is not pleasant.

Another important point in the intravenous injection is that the lumen of the needle should be free of rust. The blood in flowing out through a rusty needle is far more apt to clot than if the bore of the needle is smooth. This clot would naturally be injected into the vein in the course of the operation. I have also seen thrombus of the vein, presumably from the mere injury of the operation. The only symptoms were edema of the arm with some functional incapacity, and a cord-like hardening that cleared up in a short time.

An annoying feature, although a fleeting one, is the severe pain at the shoulder that patients often complain of after about 100 c.c. are injected. This may necessitate stopping the injection for a few moments in order to allow the circulation to readjust itself.

What is called a Herxheimer arsenical reaction may occur on the skin in the course of the first few days. It is a bright red erythema, usually best observed on the trunk, and I have never seen it give rise to any further disturbance. It is as well to know of its existence, however, as misunderstandings may otherwise occur.

The salvarsan reaction in the syphilitic lesions themselves is highly important. When, for example, there are a great number of very active syphilitic lesions, as in early malignant syphilis, the temperature reaction may run as high as 105 F. It is, therefore, important to be careful when there are many lesions, and when there is a low cachectic condition. I have never seen any deaths arise from this source, but at times there are serious inconveniences. In such cases Schreiber advises giving half the usual dose, followed in a week by the other half. Usually, the temperature reaction comes on quite early in all syphilitic lesions excepting those of the central nervous system. The temperature reaction in lesions other than those of the central nervous system occurs at about four or five hours after the injection, while in lesions of the central nervous system it occurs at about from eight to ten hours afterward. This difference is so regular in its occurrence that it may be used for diagnostic purposes. When no syphilis is present, no temperature reaction occurs. The experience of Schreiber is particularly interesting in this respect. Knowing how frequently arsenic is prescribed in psoriasis, and how excellent the results sometimes are, and knowing also that in many instances the favorableness of the result bears some relationship to the size of the dose, he hoped to achieve success in psoriasis by injecting salvarsan which contains such an enormous quantity of arsenic. The psoriatic patients injected showed no temperature reaction whatever, nor had the drug the least effect on the eruption.

There is not alone a temperature reaction in cases of syphilis in which salvarsan is injected, but there is a marked reaction in the lesions themselves. They become redder and more swollen. The drug acts in this respect somewhat like tuberculin in tuberculosis. As may readily be seen, this is an important matter when it comes to the question of administering salvarsan where the affected organ is of great dignity, as in cases of

gumma of the heart or of the brain. If a patient has gumma of the brain, from which he is suffering severely from the pressure of the tumor, the sudden enlargement of this tumor, consequent on the local reaction, may be of the greatest importance. For the same reason, if a patient has gummatous softening of an artery, giving rise to an acutely dilating aneurysm, a dose of salvarsan by increasing the quantity of blood sent to the part may cause irremediable damage. The action of mercury and of potassium iodid is quite a contrast to this, as under these remedies there is no increased afflux of blood to the affected part, but rather a slow melting down of the syphilitic infiltration. Of course, in a patient suffering with aneurysm the drug would not be administered intravenously, as the fluid itself would dangerously raise the arterial pressure.

Finally we come to a disadvantage in the administration of salvarsan, which may count for nothing in an altruistic or scientific sense, yet from a practical point of view is of great importance. It is not a remedy to use in office practice or in an ambulatory clinic. The patient should be sent to a hospital, and this in itself constitutes an expense which many patients cannot afford. Even when given intramuscularly or subcutaneously, the administration of salvarsan consumes considerable time, and the physician's time counts for something. When given intravenously a very considerable amount of time is consumed, as the administration amounts to a surgical operation, making its administration still more expensive. This expense the patient might cheerfully undergo if the physician were able to assure him that his troubles would thereby be ended, but we are far from being in a position, even after several injections of salvarsan, to assure the patient that he is permanently cured. In the present state of our knowledge, we still are compelled to advise the patient, although he has taken salvarsan, to take mercury and potassium iodid also.

An enumeration of the disadvantages of this new drug serves only to throw into still bolder relief its great advantages. The wonder grows that such a powerful spirillicide can be thrown in such quantities into the circulation with such little risk to the host. In contemplating this marvel, we begin to appreciate the fine scientific imagination of the man who made this possible.

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## ABSTRACT OF DISCUSSION

### ON PAPERS IN THE SYMPOSIUM ON SYPHILIS

DR. D. W. MONTGOMERY, San Francisco: I agree with Dr. Fox that it is unnecessary to dissolve salvarsan in normal salt solution. It is best dissolved in warm distilled water. But salt solution should be injected into the vein before injecting the salvarsan solution, in order to make sure that the point of the needle lies free in the vein. The making of the salvarsan solution is a most important step. The solution should be perfectly clear. I never saw Schreiber give the actual injection, but on the other hand I never saw this drug administered in Schreiber's clinic when he did not himself personally superintend the making of the solution. One of the speakers has accentuated a fact that I think cannot be successfully disputed, that mercury is a true specific for syphilis and that it constitutes the best means that has yet been found for treating the disease. I also believe that iodid of potash is a specific for syphilis, although inferior to mercury. Mercury is a poison. This, to my mind, is as clear as any fact in therapeutics.

DR. HOWARD FOX, New York: In our work at the New York Skin and Cancer Hospital we have observed one case of herpes zoster following the use of this drug. In the course of 128 injections we have not had any serious ill effects. In two of the cases the treatment was followed by a general toxic erythema, accompanied by high temperature, lasting three days. Necrosis at the point of injection occurred in five cases, twice after subcutaneous injections, once after an intramuscular injection of an alkaline solution, and twice after intramuscular injections of oily suspensions. I cannot agree with the previous speaker that the intravenous injection of salvarsan is a difficult or complicated procedure. With a little experience the proper introduction of the needle into the vein can readily be learned. It is hardly necessary to say in addition that the usual aseptic precautions should be strictly observed. In the interest of simplicity I think it best to use sterile water instead of physiologic salt solution for diluting the salvarsan. Furthermore, the gravity method is in my

opinion much simpler than the method originally suggested by Schreiber. In the course of sixty-nine intravenous injections we have noted the appearance of small nodules in the vein in eight cases. In six of these cases the nodules disappeared very shortly after the injection.

DR. W. J. BUTLER, Chicago: In regard to the treatment of the disease under consideration, I wonder if we all have similar ideas on this question. When is syphilis cured? I do not think that any of us can answer that question; I do not think that we can saturate a patient for two or three years and then say that the patient is cured; we all know that he is not cured. I agree with what has been said regarding the value of mercury; I can also see certain advantages that result from the administration of this agent hypodermically. How do you know when a patient is saturated? This we do not know clinically. Too much importance has been given in past years to the disappearance of external manifestations and their continued absence in judging the results of treatment of syphilis. The possibility of visceral syphilis existing or appearing at any time should always be kept in mind. I cannot emphasize sufficiently strongly the above points. If we ask ourselves when are these patients cured, we can only say, recollecting the possibility of recurrence at any time, they are cured when they are dead. We can, however, determine the activity or inactivity of the specific virus in a syphilitic by resorting to the serum reaction for syphilis. This is the only means of judging early activity of the specific process in internal organs, before clinical symptoms have manifested themselves. In the treatment of syphilis the serum reaction should not be applied for one, two or three months, or even years, but indefinitely as a control on the activity or abeyance of the disease. We should never assume that we can treat a patient with this disease for two or three years and then say positively that he is cured. The serum reaction should be resorted to when treating these patients to see that the treatment is being pushed sufficiently. We should never assume that a cure has taken place because there is a negative reaction. Such patients should not be allowed to go out of the care of the physician even when the serum reaction is negative after two, three or four years of treatment, but should occasionally receive further treatment to protect them against recurrences, and their blood should be examined three or four times a year. When found positive, treatment should be resumed.

DR. C. F. HOOVER, Cleveland, Ohio: During my student days I was profoundly impressed by an autopsy on a young man who died from pulmonary syphilis shortly after his return from Switzerland where he was sent six months before on account of an hemoptysis supposedly of tuberculous origin. Ever since that experience I have endeavored to avoid such a diagnostic error by always considering the possibility of

syphilis whenever a chronic pulmonary disease is under consideration. Thus far I have seen only three instances of pulmonary syphilis in adults. That it does not oftener occur seems strange, but it seems more strange to me that our colleagues who practice in regions frequented by tuberculous patients have not a goodly number of cases of pulmonary syphilis to report.

Every variety of fever curve is encountered in syphilis. I remember one instance in which the rise from normal to 106 F. and return to normal was accomplished within a few hours. There were sufficient signs to show that the disease was located in the liver and on account of the extremely rapid rise and fall of temperature a diagnosis of suppurative pylephlebitis was made. This patient promptly recovered after mercury was given. Another patient with syphilitic fever (whom I saw through the kindness of Dr. Buswell of Buffalo) had relapsing fever for a period of fourteen years and during all that period never had more than ten consecutive days without having at least one or two days of fever. Recently a woman who was referred to the medical ward of Lakeside Hospital from the gynecologic service had a daily evening rise of temperature to 104 F. This patient was infected with syphilis ten years previously and had been often treated for some manifestation of the disease since that time. Within forty-eight hours after mercury was given in large doses all fever ceased.

I think the experience we have had with salvarsan has taught us that the proper method of employing mercury is to give large doses up to the point of tolerance for short periods of a few weeks. Lesser doses of mercury are probably harmful when long continued.

Dr. Harry Reeves Olliver, San Francisco: I have had one case of lung syphilis, in a young man 34 years old. He had been treated for six years for tuberculosis of the lungs. He had been sent to different climates. He had had hemorrhages, but no tubercle bacilli were ever found in the sputum. About six months ago he came to me to see if I could find any tubercle bacilli. He was very despondent. When in the laboratory I questioned him; he was asked if he had ever had syphilis. He smiled and revealed a perfect set of Hutchinson's teeth. The Wassermann reaction was positive. He was placed on mercury and the improvement was rapid. The radiographic plates showed pulmonary lesions. At this time salvarsan came into use and the patient was given injections, beginning them on January 8. The improvement that followed was remarkable. He gained 19 pounds in weight in three weeks; his gain was steady. The day after his first injection of salvarsan he did, however, have a hemorrhage. So far as I can determine he is now in perfect health. Subsequent *x*-ray examinations of the thorax have shown that the shadows have markedly decreased in size. This man had a

sister with large glands over her body and I suggested that an examination of her blood be made. The Wassermann reaction was positive and, I gave her salvarsan; within two weeks the enlarged glands had entirely disappeared, and she quickly gained in weight.

The mother of these two individuals was in bed with a very pronounced myocarditis. Her blood also gave a positive Wassermann reaction. On questioning her I learned that her husband had died with evidences of a brain tumor. I think that the history in this case was complete.

I have seen four cases of nephritis in which a very large percentage of albumin and granular and hyaline casts in the urine, general anasarca, ascites, etc., were present, and these patients all made a good recovery under the use of mercury and salvarsan. The first patient was to me of particular interest. She was a young woman with general anasarca, ascites, 1 per cent. albumin and with a tumor in the pelvis. I placed her on mercury and Epsom salts. The albumin dropped to 0.1 of 1 per cent. and the casts rapidly disappeared and she greatly improved. She was operated on by Dr. George B. Somers and an ovarian cyst was removed. Ether was the anesthetic used. After the operation she had considerable pain in the back and legs; this was supposed to have been due to this tumor. After the removal of the tumor, however, the pains continued. She was a frail woman and I hesitated to give her salvarsan. The pain continued so severe, with no relief in spite of the mercurial rubs, that I decided at last to give her salvarsan. Four-tenths of a gram was given and within twenty-four hours she had no pain; it is not three weeks since the injection was given and she has not had any pain since. The patient has remained well and gained in weight.

The second case was one that appeared in the medical clinic with sciatica which had persisted for fourteen years. There was a positive Wassermann reaction. The use of salvarsan entirely cured her in a few days.

With regard to what has been said about the dosage of mercury I agree entirely, the best and most lasting results being thereby obtained. As to the saturation guide, I think we should give the full dose for twenty days and then make a Wassermann reaction test. If this is negative we have probably reached the saturation point. We should then keep the dose of mercury at this point; but if there is any indication that there is not enough mercury given, the dose should of course be increased until the Wassermann reaction is negative.

In regard to salvarsan, the resulting reaction depends on the amount of infection before salvarsan was introduced. If a patient has but a mild infection, the quicker will he become negatived after the salvarsan injection. The more positive the reaction before the introduction of salvarsan, the longer will it take for him to become negative to the Wassermann reac-

tion test. I think this is explained by the fact that a large number of spirochetes are killed and thrown into the circulation where their endotoxins give rise to the formation of antibodies. Consequently the more spirochetes present, the stronger will be the reaction and the longer the time required for their elimination from the blood.

DR. HARVEY G. PARKER, Portland, Ore.: It is interesting to note the large sums of money advised to be spent in Wassermann tests during the treatment of lues, one of the speakers mentioning sufficient to count into the hundreds of dollars, at $25 per test; it seems to me the essential thing is to treat the patient very thoroughly and when satisfied that this has been done, after waiting a period of three months without treatment, try the Wassermann test; if negative, later try another. The more frequently early Wassermanns are disregarded and all effort placed on saturating treatment, the better permanent results we will get in treatment. In line with some of the cases reported of long standing hidden syphilis, undiagnosed, I wish to report a case. A patient came to the coast under the advice of his physician who pronounced him tuberculous. He had a severe cough, loss of weight, rapid breathing, and yet expectorated very little; he wandered about from place to place and finally, quite at the end of his resources, he arrived in Portland. He gave a history of a soft chancre eighteen years previously, and was satisfied that there had been no infection since. On general principles among the things resorted to to give relief from the severe cough was protoiodid of mercury; he got some relief but fell dead in a lodging house about this time. Post-mortem revealed a gumma of the arch of the aorta with the right lung also involved. The giving way of the arch caused death. In regard to some of the skin eruptions following the use of salvarsan, I have noticed two erythematous eruptions of a bullous type appearing after the injection, one after the second dose of the drug and aggravated after the third. In another case, on the third day after injection, there developed an itching, oozing eruption, somewhat like psoriasis in appearance as far as color and elevation go, in spots from a dollar to a half in size; at the end of three weeks under astringents it disappeared. I have given salvarsan in several cases in which there was an apparent idiosyncrasy against mercury; also in cases in which mercurial treatment had been long and carelessly used with practically no results, getting gratifying and rapid results with, so far, no bad results. I heartily speak for the intramuscular injection of salvarsan, especially in old cases, but always in conjunction with proper mercurial treatment.

DR. WILLIAM LITTERER, Nashville, Tenn.: I take issue with the statement that salvarsan produced no reactions in cases other than syphilis. I have observed the use of salvarsan in five cases of pellagra, and in three marked reactions were obtained. In one the reaction was very severe, the tempera-

ture going to 104 F. while in the other two the temperature reached 102 F. All gave negative clinical history as to syphilis as well as a negative Wassermann. I have also used salvarsan intravenously in two cases of sarcoma; in one only was there a slight reaction. The patient vomited twice the next day while the temperature was 100 F. The Wassermann test was negative. In two cases of psoriasis, salvarsan was given intravenously with the result that in one case the temperature went to 99.8 F. two days after its administration. The Wassermann test was negative. In the pellagra cases good results followed its administration in one case only. In all of the others the general nutrition was improved, but there was no permanent improvement. I should like to report a unique case, which I believe to be one in which Ehrlich's "therapia sterilizans magna" was attained. This patient gave a typical clinical history of chancre on the penis. *Spirochetæ pallidæ* were found in large numbers three days after the appearance of the primary lesion. The Wassermann was negative. The chancre was excised and the spirochetes were demonstrated in the tissues by the Levaditi stain. After the method of Iversen, an intravenous injection (0.5 gm. salvarsan) was given, followed four days later by another (0.5 gm.) intravenous, and five days later an intramuscular injection (0.6 gm.) by Lesser's method was given. No other antisyphilitic treatment was instituted. The patient felt perfectly well in every respect. Wassermann tests were made every month for ten months with negative results. Three weeks ago this patient developed another chancre on the penis, which came nineteen days after a suspicious intercourse. The chancre was typical in every respect and numerous spirochetes were found in the lesion. One intravenous of salvarsan caused its disappearance in two weeks. To my mind this is a case in which the first three doses of salvarsan produced a complete sterilization of all the spirochetes in the body. Ten months elapsed without the slightest symptoms and repeated negative Wassermann tests were always recorded. The appearance of the second chancre is a probable demonstration of an instance of Ehrlich's "therapia sterilizans magna."

DR. GEORGE H. AIKEN, Fresno, Cal.: I should like to say something from the standpoint of the general practitioner. I have been treating syphilis for over thirty years and have had a large number of cases. I feel somewhat humiliated in being told that I have really never cured a patient. I rise especially to ask the gentleman who says that no patient is ever cured to listen to the recital of this case: A young man 20 or 25 years old, having been treated for this disease for two years, marries a healthy young woman, who bears four or six children. These children grow up healthy and strong, they never develop any local or constitutional evidences of syphilis, and they are under observation constantly for over twenty years. What should be our conclusion in this case? Was this patient not cured?

DR. WILLIAM W. GRAVES, St. Louis: If there is anything the medical profession of this country is united on, it is the belief in the curability of syphilis; yet recent serologic investigation and more accurate clinical observations indicate that many individuals whom we have considered cured have not been cured at all, and this is true whether from our recognized specific or from the much lauded salvarsan. Aside from accurate clinical studies of the syphilitic, similar studies of his wife and his progeny further show the inadequacy of our therapy. During the last five years I have made what I have called comparative clinical studies of families in which the fathers were syphilitics; likewise of families in which the fathers were free from syphilis. These studies have shown what is everywhere recognized, that healthy parents beget offspring, as a rule, quite equal to themselves in physical and mental endowments. "A chip off the old block" is expressive of our expectation of the offspring of healthy parents. My studies of families in which the fathers were syphilitic have shown: first, the wives, like the husbands, are rarely free from some of the more subtle manifestations of syphilis, such as pupillary anomalies, sensory loss, arterial changes, pallor, alterations in reflexes, etc.; second, the offspring rarely compare favorably with either parent or with each other. These studies have further shown the infrequency of the heretofore recognized signs of congenital or so-called hereditary syphilis, such as Hutchinson's teeth, interstitial keratitis, deafness without otitis, joint, skin and mucous membrane affections. Now the absence of these signs is one of the main props to our belief in the curability of syphilis. When such signs fail in the progeny, we point to them as living examples of the triumphs of our therapy in the parents. Similar comparative clinical studies of a few families in which the fathers are tabetics or paretics or known syphilitics will prove to anyone who will take the time to make such studies the inadequacy of our therapy, and, at the same time, the evil effects of syphilis on the progeny. I wish to indorse all that has been said by Dr. Butler. We must look the issue squarely in the face and not be afraid to look more closely at the progeny and to make clinical studies of them and of their mothers. We consent to a syphilitic's marriage three, four or five years after his infection, provided he has had adequate treatment and no recent manifestations; yet no man can say when a syphilitic has had adequate treatment nor when he is cured. The repeated use of the Wassermann reaction indicates that not more than 35 per cent. are apparently cured, and more accurate studies of the syphilitic, his wife and progeny will show that he is seldom, if ever, cured. It is safe to say that not more than 10 per cent. of syphilitics who apply to the medical profession for treatment receive what is considered adequate treatment; so that Nature must take care of the 90 per cent., and comparative studies of families will show that she does it almost as

well as we do. These studies have caused me to admire Nature's resources in the care of syphilitics and at the same time to believe that our hope for a cure lies neither in mercury nor salvarsan, but in prevention.

DR. B. H. ORNDORFF, Chicago: I wish to relate the experience I have had with salvarsan. In a series of nearly 100 cases of syphilis intravenous injections of salvarsan were given and without any unfavorable symptoms. In nearly all of the cases the Wassermann reaction test was positive. I also gave salvarsan in three cases of leukemia. The first was a case of myeloid leukemia, with 450,000 white cells. The full dose was given. There were no beneficial or deleterious effects for about three months following the injection; then the patient had trouble with the auditory apparatus. This patient died one month later when he was totally deaf. The second case was one of lymphatic leukemia with 600,000 cells of the mononuclear type. Three weeks following the injection of salvarsan, this patient died, having slight auditory disturbances. The third case was one of chronic lymphatic leukemia; the white cells were less than 200,000. No advantageous nor deleterious results followed the injection of salvarsan.

DR. L. S. SCHMITT, San Francisco: The discussion has been somewhat apart from the subject of my paper, the laboratory diagnosis of syphilis. By using laboratory methods, particularly the dark-field condenser, one can corroborate the point made by Dr. Graves that the injection of salvarsan reduces the contagious condition of the initial lesion, and of the secondary syphilids within twenty-four hours. With regard to the point brought up by Dr. Butler, it is difficult to tell when a patient with syphilis is cured. In the examination of the serums of the offspring of syphilitics I have found positive reactions in a number when there were no clinical manifestation in the parents. In syphilis, with a return of the reaction one can anticipate a return of the clinical symptoms. To bring out a point made by Dr. Graves and Dr. Butler, I have in mind a patient who without doubt had syphilis; the Wassermann reaction made shortly before death was positive. The history brought out the fact that the primary sore dated back forty-one years before his death.

DR. FRANK BILLINGS, Chicago: Visceral syphilis is very prevalent in the large cities, but is not much found in the country towns. There is no doubt that any man who has access to the big hospitals will find many cases of visceral syphilis, cases that have not been discovered previously. Dr. Hoover mistakes me when he states that I said I had never met with a case of pulmonary syphilis. I did say, however, that I had never seen cases that were called in the literature "interstitial forms of pneumonia of the syphilitic type." Such cases I have not seen. I believe Dr. Graves' statement is true, that probably a very small portion of people applying for treatment are

properly treated. Therefore, late syphilitic lesions are presented to us. How many of you have cases of locomotor ataxia come for treatment and in taking the history you find that the patients have not had adequate treatment? How many of you have found locomotor ataxia develop among your own patients? I have practiced medicine over thirty years and I have seen many patients with visceral and nervous syphilis who have not been cured. Perhaps I have not cured these patients. Can any of you say that your malarial patients are cured? Yet I do not want our old friends and patients to believe that one suffering from syphilis will be condemned to an eternal attack of this disease. I believe enough in drugs to feel that mercury will absolutely cure syphilis. If I can keep patients long enough under observation, I believe I can prevent further signs of the disease appearing. I have had some experience with salvarsan chiefly in late syphilis. I have given salvarsan to thirty-three patients. I have repeated the dose in several patients. One patient received four doses. Three patients each received two doses. The results from the use of salvarsan have not been as good as from the use of mercury in my hands. In patients suffering from locomotor ataxia salvarsan seems to have an analgesic effect. Those suffering from the crises seem to be relieved in a few hours after receiving this agent. I recall one man who came from Milwaukee with a very severe neuritis of the brachial plexus; he had been confined to his bed for many months; the Wassermann reaction was positive. This patient was entirely relieved of his pain in eighteen hours and he was able to use his hand again within one week after the injection. I have seen many instances which show the analgesic effect of salvarsan. I believe in the use of mercury. As to what form of mercury to use I believe that is, to a certain extent, a matter of individual choice. During the last few years I have come to resort to the intramuscular method; I feel that I can command the dosage better in this way than in any other. I can keep my patients better under command. I think the value of mercury is greatly enhanced when the patient is absolutely at rest; this applies to any case of syphilis, whether primary or late. Mercury should be pushed to the point of saturation; this means at least to the point of salivation. I give large doses—as much as one-half a grain of corrosive sublimate; by repeating this again and again we conserve the best interests of our patients. I look on the iodids not as a specific in any sense, but as a helpful means of driving out the waste material. When we meet with gumma, for instance, the administration of the iodids will clear it up quickly as a rule, and without intervention from mercury.

# HEMORRHAGIC EROSIONS OF THE STOMACH

## WITH THE REPORT OF THE AUTOPSY FINDINGS IN A CASE OF EINHORN'S DISEASE

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Hemorrhagic erosions of the stomach from the viewpoint of the examination of the fasting organ is not an infrequent clinical finding. In 600 consecutive cases in which this routine examination was made as a part of general diagnosis, there were thirty-five cases, or 5.8 per cent., in which definite erosions of the gastric mucous membrane were found. As shown by the accompanying table, these cases were divided among the following disease conditions: Pernicious anemia, general asthenia, carcinoma of the stomach, carcinoma of the esophagus, cardiospasm, cardiosclerosis, dyspepsia nervosa, Schmidt's fermentation dyspepsia, Einhorn's disease, chronic anacid gastritis, chronic subacid gastritis, chronic acid gastritis, chronic gastrosuccorrhea, chronic gall-bladder disease, chronic intestinal catarrh, spastic obstipation, chronic salpingitis and chronic ulcer of the stomach. Two cases of so-called simple erosion, characterized by sudden severe gastric hemorrhage, afforded no fragments of mucous membrane either by vomiting or later by examination.

From a study of these cases the erosions group themselves logically into, (1) those without clinical significance, and (2) those with positive clinical significance.

Into the first group are placed the fragments of mucous membrane which are, for the most part, accidentally recovered. Chronic gastritis, together with the

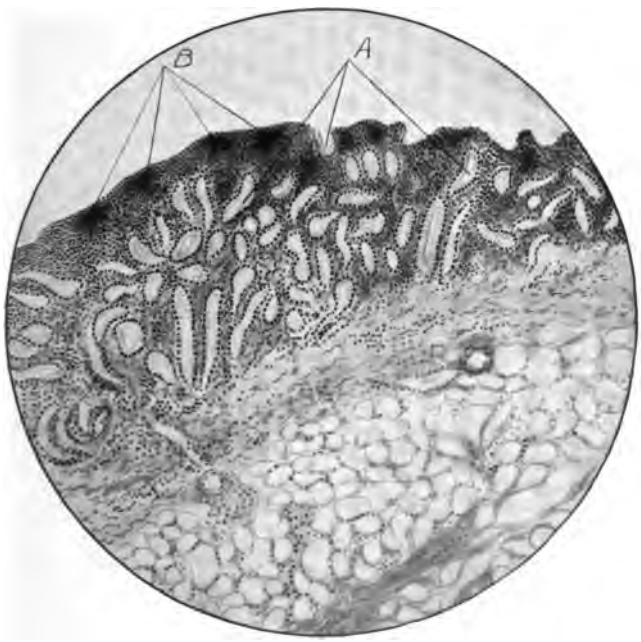
muscular contractions of the stomach and the trauma from the tube, has afforded thirteen of thirty-four cases. This trauma, together with the contractions of the muscular coats, has seemingly been the entire cause in all of the remaining cases with the exception of the two malignant ones, in which erosions were found. It has been noted also that these erosions were obtained only where there was more or less retching and resistance on the part of the individual. Study of most of the fragments in teased preparations or from sections, in those instances in which the erosions were large enough to be so treated, has not thrown any further light on their etiology. There is always a variable amount of small round cells between the gland acini, but it has been quite impossible to distinguish between round-cell infiltration and normal lymphoid structure. In one large erosion from a case of subacid gastritis "the cuticula and crypts were not broken or disintegrated, but in the deeper portions of the glands the cytoplasm stained faintly and was swollen. In places it seemed to be disintegrating and portions of the glands were missing. There was some small round-cell infiltration, but nowhere was it of marked degree." Other etiologic factors determined by Mintz, Wurtz and Leudet, Dieulafoy, Nauwerk, Gerhardt, Langerhans and E. Fraenkel, were not found.

There are, however, two types of hemorrhagic erosions of the stomach of distinct clinical importance, which present fairly definite clinical pictures. They are (a) the so-called simple erosion of Dieulafoy and (b) the chronic and recurring type of erosion described first by Einhorn and now termed Einhorn's disease.

Of the simple erosion, which is characterized by sudden, severe, at times fatal hemorrhage occurring during normal health, usually without pain and with but little sickness, I do not wish to speak, excepting to emphasize the need of a better recognition of the condition and the employment of rational medical treatment. In one of

the four cases seen by me death was hastened, if not actually caused, by surgical measures, and two of the three other patients were strongly urged by competent operators to submit to operation. I think it is now quite agreed among surgical writers as well as among physicians that acute bleeding from the stomach is a condition best handled by medical means and not by surgery. In 1901 Rodman reported thirty-two operations for acute gastric hemorrhage with nine deaths, a mortality of 40.6 per cent. In 1906 Laurent reported 93 per cent. recovery in his patients treated medically. A critical review of the literature since these dates bears out this contention more forcibly, and yet such patients are still being operated on. This fact, in my opinion, justifies the clinical grouping of this class of cases in such a way as will emphasize the importance of their treatment whatever the pathogenesis underlying the condition may be.

According to Einhorn, the disease which was described first by him in 1894, and which now bears his name, is a chronic condition characterized by diffuse stomach pain which comes on shortly after eating and is not influenced by pressure, vomiting or eating again; by a sense of great weakness, a rather rapid loss in weight, and, pathognomically, by the repeated presence of from two to four erosions in the wash water from the fasting stomach. Einhorn's belief that this clinical picture was the expression of a distinct disease has been upheld by Mintz, Berger and others. Pariser, Nauwerk and Elsner, on the other hand, have maintained that the basis of the picture has been a chronic gastritis, the ordinary symptoms of which have been forced into the background by the periodic occurrence of the erosions and the bleeding. Owing to the entire absence of post-mortem examinations of such cases, the following typically illustrative case which came to autopsy is given briefly in detail, together with the anatomic findings:




**Reproduction from drawing showing histologic characteristics of tissue. A, remnants of gland acini; B, blood extravasation in areas of dense, small round-cell infiltration.**

*History.*—Mr. D., a business man, aged 57 years, began twenty years ago to have, with the coming of each winter, periods of illness characterized by a diffuse sense of burning in the stomach after eating, sometimes on rising, a rapidly developing weakness, paleness and loss of weight. At times there was some nausea and the regurgitation of clear fluid which was not especially sour to taste. All foods produced distress. There was no local tenderness, no fever, chills or sweating. The bowels were regular. Each year the illness lasted several weeks, usually in bed with restricted diet. More or less paleness and weakness would last until warm weather set in, when he would regain his health rapidly, his anemia would disappear and his stomach would again tolerate any kind of food without discomfort. The patient believed a causal relationship existed on the part of the cold and always dreaded the approach of winter. During the illness of the year preceding that of his death occult blood was found in the stools. His last illness came on as they always had before and was of several weeks' duration. Blood was again found in the stools. Dr. Mackenzie tells me that blood examinations showed a very severe grade of a chlorotic type of anemia. The patient had weighed 202 pounds before his illness began but had lost much flesh during it. His own personal history and that of his family were negative in all respects.

*Necropsy.*—Through the courtesy of Dr. Mackenzie I made a post-mortem examination on Dec. 20, 1909, six hours after death. Briefly the anatomic findings were as follows: The body was that of a tall, heavily boned, greatly emaciated middle-aged man. The panniculus was pale and scanty; the peritoneum was smooth and glossy. All parenchymatous organs were very pale and dry. The heart and lungs were otherwise negative. Very small scattered atheromatous patches existed in the beginning of the arch of the aorta. They were absent throughout the course of the abdominal aorta. There was no gross evidence of terminal infection. The bone-marrow of the ribs was pale in color. The intestine and colon were more or less filled with dark, tarry content that contained much blood. The stomach was of normal size, blanched, and contained a little turbid fluid. Over the mucosal surface a moderate amount of greyish, somewhat blood-stained, tenacious mucus was found. On the posterior wall about midway between the cardia and the pylorus were seen five small eroded areas with hemorrhagic margins and bases. They were superficial in character, not extending to the submucosa, and varied from the size of a split pea to 1.5 cm. in length and ⅓ cm. in width. No eroded vessels could be found.

The stomach was given to Dr. Roberg of the medical department of the University of Oregon for histologic examination. He reports as follows:

The mucosal surface of the organ is pale yellowish in color, mottled by several deeply colored and rather circumscribed areas. Sections for examinations were taken through both the pale and the darker portions of the stomach-wall. Microscopically, the dark areas show no difference in appearance from the other. They are pigmented areas of submucous hemorrhages, the coloring of which is derived from dissolved hemoglobin deposited in the interglandular tissue and in the secreting cells of the gastric glands. The interstitial tissue of the epithelial layer of the mucosa is the seat of a dense, small round-cell infiltration. This infiltration is diffuse and more marked in the surface of the mucosa. The deposit of these small round cells is so dense that in many cases the stomach glands have been completely obliterated. Scattered throughout this dense infiltration are islands or portions of glands. Their lumina are distended to two or three times the normal size. The cell cytoplasm is granular and disintegrated and in many places the lumina are filled with a cytoplasmic debris. In the fundus region no differentiation of the gland cells occurs into parietal and chief cells. All gland-cell nuclei stain less deeply than normal. The capillaries in the mucous membrane are markedy dilated along the basement membrane and, in the region of the crypts, show a diffuse extravasation of blood. The blood-vessel plexuses in the submucosal and muscular layers show a thickening of the walls and a slight congestion. The muscular layer, submucosa and muscularis have to a slight degree an infiltration of small round cells.

I submitted also to Dr. Roberg for histologic examination three large erosions from a typical case of Einhorn's disease which I have had under observation for over three years and which I have previously reported. His findings are as follows:

The gastric crypts and cuticular border of the mucosa are quite intact. The neck and fundus portions of the gastric glands are displaced and partly obliterated by a small round-cell infiltration not unlike that described in the previous case but not so dense. The destruction and displacement of the glandular elements, although considerable, are likewise not so marked. Interstitial hemorrhage and congestion are absent.

Thus the microscopic examination of the two cases presents the picture of a form of chronic gastritis characterized (1) by a dense small round-cell infiltration in the interstices of the

TABLE OF SIX HUNDRED CASES AND RELATION OF STOMACH EROSIONS TO THEM

| Disease. | No. of Cases. | Cases with Erosions. | Erosions Found in Each. |
|---|---|---|---|
| Anemia, pernicious | 4 | 1 | 2 |
| Anemia, metasyphilitic | 1 | 0 | 0 |
| Anemia, chlorosis | 1 | 0 | 0 |
| Aneurysm abdominal aorta | 2 | 0 | 0 |
| Appendicitis, chronic | 3 | 0 | 0 |
| Abdominal arteriosclerosis | 4 | 0 | 0 |
| Arthritis, toxic | 3 | 0 | 0 |
| Asthenia, general | 79 | 1 | 4 |
| Brain tumor | 1 | 0 | 0 |
| Carcinoma, stomach | 18 | 1 | 2 |
| Carcinoma, pancreas | 1 | 0 | 0 |
| Carcinoma, sigmoid | 3 | 0 | 0 |
| Carcinoma, liver (*sec*) | 1 | 0 | 0 |
| Carcinoma, esophagus | 1 | 0 | † |
| Colitis, mucous | 24 | 0 | 0 |
| Colitis, chronic ulcerative | 2 | 0 | 0 |
| Cardiospasm | 7 | 2 | 2, 2 |
| Cardiosclerosis | 15 | 1 | 1 |
| Cirrhosis stomach | 1 | 0 | 0 |
| Dyspepsia nervosa | 11 | 1 | 1 |
| Dyspepsia fermentation (Schmidt) | 13 | 2 | 2, 1 |
| Diabetes | 1 | 0 | 0 |
| Erosions of the stomach (Einhorn's disease) | 1 | 1 | 4 |
| Erosions of stomach (simple hemorrhagic) examined late after bleeding | 2 | 0 | 0 |
| Epilepsy, *petit mal* | 1 | 0 | 0 |
| Fibroid right broad ligament | 1 | 0 | 0 |
| Gastritis—chronic anacid (inc. achylia gastrica) | 47 | 6 | †1, 4, 2, 1 |
| Gastritis, chronic subacid | 22 | 3 | 1, 2, 3 |
| Gastritis, chronic acid | 13 | 2 | 1, 2 |
| Gastrosuccorrhea, chronic | 23 | 2 | 1, 1 |
| Gastrectasis (without ulcer) | 11 | 0 | 0 |
| Gastroptosis | 12 | 0 | 0 |
| Gastromyxorrhea | 1 | 0 | 0 |
| Gall-bladder disease, chronic | 29 | 3 | 1, 1, 2 |
| Hyperchlorhydria | 8 | 0 | 0 |
| Hypochlorhydria | 3 | 0 | 0 |
| Hypertension, arterial chronic | 2 | 0 | 0 |
| Intestinal catarrh, chronic | 22 | 1 | 1 |
| Myatonia congenita | 1 | 0 | 0 |
| Migraine, chronic | 4 | 0 | 0 |
| Nephritis, chronic | 3 | 0 | 0 |
| Neurasthenia | 31 | 0 | 0 |
| Obstipation, atonic | 31 | 0 | 0 |
| Obstipation, spastic | 69 | 3 | †1, 1 |
| Organic heart disease | 11 | 0 | 0 |
| Polycythemia | 1 | 0 | 0 |
| Pyloric insufficiency | 4 | 0 | 0 |
| Salpingitis, chronic | 1 | 1 | 1 |
| Sacro-iliac joint relaxation | 1 | 0 | 0 |
| Scoliosis | 1 | 0 | 0 |
| Tuberculosis, lungs | 7 | 0 | 0 |
| Tuberculosis, peritoneum | 1 | 0 | 0 |
| Tabes | 2 | 0 | 0 |
| Ulcer of stomach, chronic | 31 | 3 | †1, 1 |
| Ulcer of stomach, healed | 2 | 0 | 0 |
| Ulcer of stomach, duodenal | 2 | 0 | 0 |
| Urticaria univ | 1 | 0 | 0 |
| † Many. | 600 | 35 | |

glandular elements, which when extensive obliterates the gastric glands by pressure; (2) by the disintegration of the cuticular portion of the mucosa as the crypts are displaced by the small round cells; and (3) by the fact that with the disintegration of the cuticula and crypts the congested vessels are exposed and ruptured, which accounts for the gastric hemorrhages occurring during the clinical course of the disease.

An entire absence of proliferation of the connective tissue elements, the engorgement of the superficial blood capillaries and the manner in which the gland cells are destroyed sharply differentiate the process from ordinary chronic gastritis. The claim, therefore, of Elsner and others that the disease is one of ordinary gastritis with the factor of erosion formation added to it is no longer tenable, and neither, on the other hand, is that of Einhorn, for the process must be classified as a type of chronic gastritis. It is, in fact, a chronic, non-proliferative, hemorrhagic gastritis.

In general, I believe it will be well to retain this clinical grouping of hemorrhagic erosions, and to consider them, clinically speaking, as disease entities for the sake of defining their relation to other types of gastric hemorrhage. Simple erosion, on the one hand, probably possesses a manifold etiology. Whether Einhorn's disease likewise does, only further autopsy findings will determine. From the similarity of these two cases, however, it is probable that its pathology will be found to be the same in others.

BIBLIOGRAPHY

1. Einhorn: Berl. klin. Wchnschr., 1895, No. 20; Arch. f. Verdauungskrankh., 1899, v.
2. Pariser: Med. Rev., Vienna, 1897, No. 1; Berl. klin. Wchnschr., 1900, No. 43.
3. Mintz: Ztschr. f. klin. Med., 1902, xlvi.
4. Dieulafoy: Sémaine méd., 1900 (Third International Congres).
5. Virchow: Virchow's Arch., v, 363.
6. Harttung: Deutsch. med. Wchnschr., 1890, No. 38.
7. Langerhans: Virchow's Arch., cxxiv, 373.
8. Ewald: Klinik d. Verdauungskrankh., 3d ed., ii, 35.
9. Gerhardt: Virchow's Arch., cxxvii, 85.
10. Nauwerk: München. med. Wchnschr., 1897, Nos. 35 and 36.
11. Fraenkel, E.: Virchow's Arch., 1906, p. 411.
12. White, W. Hale: Lancet, London, 1906, ii, 1189.

13. Connell, F. G.: Ann. Surg., 1904, xl, 500.
14. Connell, F. G.: Am. Med., 1905, ix, 606.
15. Connell, F. G.: New York Med. Jour., March 25, 1905.
16. Laurent, Jules: Thése, Montpellier, 1906, 47.
17. Finsterer, Hans: Die Heilk., Mai, 1910, 5, 157.
18. Lund, F. B.: Tr. New Hampshire Med. Soc., Concord, p. 110.
19. Hall, F. de Havilland: Med. Mag., London, 1909, xviii, 251.
20. Plique, A. F.: Bull. méd. Paris, 1908, xxii, 1111.
21. Duckworth, Sir Dyce: Clin. Jour., London, 1908, xxxii, 167.
22. Steinberg, Hugo: Berl. klin. Wchnschr., 1909, xlvi, 786.
23. Robson, A. W. Mayo: Scot. Med. and Surg. Jour.. Edinb., 1901, viii, 205.
24. Morton, A. W.: South Calif. Pract., Los Angeles, xiii, 8.
25. Einhorn, Max: New York Med. Jour., 1903, lxxvii, 777.
26. Berger, Cl.: Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1908, xii, 129.
27. Eichberg, Joseph: Ohio State Med. Jour., 1905, 101.
28. Engelsmann, R.: Mitt. a. d. Hamburg. Staatskrankenanst, 1909, x, 223.
29. Einhorn, M.: THE JOURNAL A. M. A., 1890, xxxii, 1079.
30. Berger, Cl.: München. med. Wchnschr., 1907, liv, 116.
31. Elsner, Hans: Deutsch. med. Wchnschr., 1903, xx, 735.

## ABSTRACT OF DISCUSSION

DR. ROBERT T. MORRIS, New York: In these days when so much credit is given to proper stomach surgery, I wish to emphasize a point made by Dr. Jones that hemorrhagic erosions of the stomach are not cases for the surgeon. Whatever credit comes to surgeons is from wise selection of cases. Surgery does not at all comprehend the question of gastric erosions and does not give relief because the original condition persists. Again, there are the shock and other features which were incidental to operation, features that are not desirable. There was one point, however, that Dr. Jones did not bring out and one which I believe to be very important. We should learn more of the early septic history, and especially of the ordinary medical treatment that was employed at the time the erosions occurred. Of course, the patients must have treatment when these erosions of the stomach occur, but the earlier toxic history should be kept track of in all these cases. We should remember that hyperchlorhydria and hypochlorhydria are symptoms like coughing or sneezing. The hormones send wrong messages to the secreting glands. What reason have we for believing that excreted toxins are basic factors in these erosions? What is found in the peritoneum of the vicinity gives us a clue? We all have found peritoneal adhesions so common in the pyloric region that we must assign some significance to them. We often meet with cases of adhesions, "cobwebs in the attic of the abdomen," which are due apparently to the excretion of toxins by the liver; in some cases the lesion might be due to the actual excretion of bacteria, chiefly of the colon-bacillus group, which pass the liver unharmed at times, but set up trouble in the bile-tract. The

endothelium desquamates, lymph is excreted, coagulation occurs and adhesions are then formed and gastric disturbances follow. These hieroglyphics most of you can read and must read. When these hieroglyphics in *bas relief* occur in the peritoneum, the "cobwebs in the attic of the abdomen," we must look for an explanation in the toxic influences preceding erosion. Such toxic influences result in spasm of the terminal arteries situated in this region. Please do not forget the terminal arteries, for we are dealing with them. The toxic spasm of the terminal arteries here results in cell infiltration and other pathologic conditions, such as Dr. Jones has described in his paper.

In the treatment of hemorrhagic erosions of the stomach, surgery should not, I believe, be considered at all; medical treatment alone should be employed; any operation in these cases must result in disaster. If we hark back to the original cause I think we shall find that hemorrhagic erosions of the stomach are the result of excreted toxins.

DR. J. F. HULTGEN, Chicago: Erosions of the stomach are not considered sufficiently in connection with the constant anemia which one meets with in these cases. This fact suggests to me that there might be an anatomic cause for this condition—the symptom-complex might be due to the anemia itself; it might be due, as Dr. Morris has suggested, to some toxic process. The anemia coexistent or coexisting in these cases has not been thoroughly inquired into; more investigations should be made in order to bring out this matter. As a matter of fact, the anatomic basis, so far as was shown by Dr. Jones, was not sufficient to explain the clinical course of the disease. I believe that the gastric hemorrhage from the erosion is nothing but a symptom, and that the underlying morbid process might be of hemolytic nature or of toxic origin.

DR. PHILIP KING BROWN, San Francisco: This condition of hemorrhagic erosions of the stomach is not recognized easily. Hemorrhage occurring in association with pain might be the result of chronic disease of the appendix, so fully described by Moynihan several years ago. He reported twelve cases, the symptoms of which were classical of gastric ulcer; at operation no ulcers were found. In each instance, however, there was found a diseased appendix. When the appendix was removed in these cases all the symptoms of gastric ulcer disappeared. It was my lot to recommend for operation practically the same kind of a case; this patient presented symptoms that made one feel quite positive of his diagnosis. The individual had been under the care of Dr. Boas and Dr. Ewald and other stomach specialists of note. They all made a similar mistake in the diagnosis. The symptoms were entirely gastric and hemorrhages were quite frequent. Under my care and while on a strict Lenhart diet, with the usual subnormal temperature,

there suddenly developed a rise of 4 or 5 degrees above the normal. Evidently there was some pathologic condition in the appendix, as the fever was accompanied by pain, spasm and tenderness at McBurney's point, but it did not seem wise to operate on her at the time. Later at operation a very careful exploration of the gastric region was made, but nothing was found at all. The appendix was examined and removed, because adjacent to it was found a calcified gland and there were other evidences of old disease of this organ in the way of firm adhesions and partial occlusion and thickening. No really satisfactory explanation of the cause of hemorrhage from the stomach in these cases has yet been given. Whatever statements have been made thus far are not at all satisfactory to those who are looking for an explanation, but the point of gastric hemorrhage without ulcer from disease of the appendix is well established and should be borne in mind.

DR. N. W. JONES, Portland, Ore.: In an exhaustive search of the literature on Einhorn's disease there are found no records of cases coming to autopsy. The pathology of the case reported by me seems to be distinct, but it needs verification by other cases. This condition is entirely distinct from those septic conditions in which stomach bleeding has occurred, as reported by Moynihan and Dieulafoy; and, it would seem to me, can have no relation to them. Its pathogenesis is not known. It does not seem to be that of ordinary chronic gastritis.

# RESERVE RENAL CAPACITY IN CHRONIC INTERSTITIAL NEPHRITIS

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In the mid-course of chronic interstitial nephritis, with the secreting structures of the kidneys greatly reduced by degenerative and atrophic processes, more or less marked renal insufficiency is the rule. With the high-pressure circulatory balance well maintained, the urinary water flows in full or increased volume, the insufficiency being confined to an inadequate excretion of certain waste and superfluous determinable and occult substances which are deleterious to the human body, and which are ordinarily efficiently removed by healthy kidneys. It is probable that the most toxic and important of these are, as yet, demonstrable only by their effects. In the future, when methods shall have been perfected whereby these may be differentiated and measured, our problem will be susceptible of ready and accurate solution. For the present, and for our practical purposes, we are compelled to rely on the amount of urea, chlorids, phosphates and sulphates contained in the daily urine, together with the general and special symptoms, in forming an estimate of renal capacity. Notwithstanding the difficulties and inaccuracies attending such estimates under current conditions, it is my opinion, based on a fairly long and broad experience, that they are of sufficient diagnostic and prognostic importance to warrant their employment in the routine of general practice.

Many years ago I attended a man who was known to have had chronic interstitial nephritis for more than

twenty years, during the latter of these accompanied by frequent and at times very severe attacks of uremia. For several years fairly full analyses of the urine were made once or twice a week, and at times daily for periods of from two to six months. These analyses showed the total solids and urea uniformly greatly reduced, the latter ranging from 3 to 12 gm. per day, with 8 gm. as an approximate average. At one time the daily excretions of urea averaged about 5 or 6 gm. over a period of several weeks, at the end of which the patient had a severe attack of uremia with most active maniacal excitement. During twenty-four hours of violent muscular exertion he passed urine which contained 36 gm. of urea. Following this observation it was noted that active, and to a lesser degree passive, muscular exercise regularly increased the excretion of urea, and approximately a like amount of such exercise always augmented the urea excretions to a corresponding degree; that is, up to from 10 to 12 gm. Later it was experimentally demonstrated that if lean meats were added to the diet, the urea excretion was further increased according to the amount of proteid ingested, up to 15 or 20 gm. This required about 300 gm. of meat. In this case it was clearly evident that beyond this proteid intake the urea output lagged behind. For reasons not material to our theme these observations, so far as the giving of meats was concerned, were omitted, but the employment of active and passive muscular exercises were continued with satisfactory results as an important feature of management. In this case the conclusion to which I had come, and which was shared by other physicians, namely, that the secreting structure of the kidneys were so largely destroyed as greatly to reduce the renal functional capacity, using the urea output as a measure, to far below the requirements of the system, and with a practical abolition of any reserve capacity, was demonstrably erroneous.

During the past ten years I have had frequent opportunities to pursue these investigations, with the result that a sufficient array of facts has been accumulated to warrant the deduction that, in the class of cases under discussion, the kidneys are seldom anatomically or functionally altered to such degrees as to preclude the moderate regular excretion of water, urea, chlorids, and other of the measurable constituents of the urine, and, on occasions of great and extraordinary stimulation, to show evidence of correspondingly increased functional activity, which may, with propriety, be termed reserve renal capacity. That this is an important fact, capable of being turned to diagnostic, prognostic and therapeutic usefulness, must be clearly evident.

In investigating the capacity of the kidneys in chronic interstitial nephritis under the ordinary conditions of life, and under those entailing extraordinary stress on all the organs engaged in the production and excretion of the urinary constituents, various procedures may be adopted, varying with the character of the information desired, and, it may well be added, with the predilections of the physician.

The conditions under which the excretion of urinary water may vary are so fully dealt with in the literature that only a few points of practical importance will be considered: As is well known the urine is, as a rule, notably increased in quantity, with a very considerable proportional and total reduction of the urea and other solids. Should the volume of urine decline, without a corresponding reduction of liquid intake, further examination will disclose circulatory failure with occult or manifest edema. Much later, when there is added to the above high color and increased or even largely increased total urea excretion, cellular nutritive balance with destructive metamorphosis will be present. Observation will soon show that at neither the highest nor lowest output of urinary water does the excretion of urea and other solids reach the highest level; but rather is this

found at some intermediate point, which, because of its therapeutic importance, should be, from time to time, closely determined.

During the recently passed years the excretion of chlorids has been very closely studied, and I have only a word to add in this connection, namely, that as a foundation for any dietetic directions which intelligently consider this question, there should be a fairly accurate determination of the chlorid excretory capacity of the kidneys. The methods may be readily adapted.

In the present state of our knowledge in chronic interstitial nephritis, and in connection with our theme, greatest interest lies in estimating, comparatively and absolutely, the excretory capacity of the kidneys for those nitrogenous substances resulting from proteid metabolism of which urea is the chief and best known.

For the purpose of obtaining information as to the renal capacity, I am in my own practice accustomed to employ the following procedures:

The daily urine is examined closely, and recorded and charted every day during the entire time occupied in making the observations, which is divided into a series of periods of three days each. During the first of these the patient is under his accustomed diet and regimen. During the second he takes two freshly made pills of mercurial mass every night, followed by a saline cathartic next morning. In the third the diet is restricted to water, cream and water soups and thin gruels, all in moderate or small quantities, with physical rest. During the fourth he has added to his diet breads, rice and potatoes, the food having a daily caloric value to meet fully nutritional requirements. To this there is added 300 gm. of lean meat during each of the three days of the fifth period; 400 gm. in those of the sixth; 500 gm. in those of the seventh; 600 gm. in those of the eighth. If desirable, the series with increasing amounts of proteid intake may be further extended if required.

In giving the meats in this gradually ascending scale, it will be noted that during the earlier periods the urea excretion rises directly as to the proteid ingestion. As the scale ascends, however, there comes a time in which ingestion of proteids and excretion of urea no longer run parallel, the latter lagging behind; later this becomes so marked that I prefer to terminate the investigation.

Applying the rule of averages, to which no chronic interstitial nephritic patient very closely conforms, the daily excretion of urea by the three-day periods may be tabulated as follows:

Period 1, under ordinary diet and regimen.....12 gm.
Period 2, under ordinary diet, etc., with evacuants..... 8 gm.
Period 3, under very restricted diet and rest..... 6 gm.
Period 4, under full carbohydrate diet plus 300 gm. lean meat .....14 gm.
Period 5, under full carbohydrate diet plus 400 gm. lean meat .....22 gm.
Period 6, under full carbohydrate diet plus 500 gm. lean meat .....30 gm.
Period 7, under full carbohydrate diet plus 600 gm. lean meat .....36 gm.

If during the fourth and subsequent periods the patient subjects himself to unusual active and passive muscular exercise, the urea output should be considerably augmented. Should there be any material deviation in a downward direction, from the curve of urea output, based on the above, a corresponding renal incapacity is indicated; any excess above that of the first period which may be observed during periods of four to seven, inclusive, represents reserve renal capacity.

In making these tests, wide variation in methods, and in additions to or subtraction from the details of those mentioned, may be practiced, as required, or as individual experience demonstrates to be the most available. Special emphasis, however, should be laid on the character of the proteid given, inasmuch as the urea output after the ingestion of meat follows fairly promptly and reaches its full height on the second, certainly on the third, of these days, whereas should eggs be employed,

a much longer time is required for elimination. There may be added during these last three days as much active and physical muscular exercise as the patient is able to bear, which will further increase the output of urea. Personally, I prefer to make this a fourth three-day period, but this is probably immaterial.

As an example of the wide variations met with in making these estimations, the following case is worthy of mention. A few years ago a gentleman, 65 years of age, with chronic interstitial nephritis of many years' duration, passed, under great urinary stress, urine which contained during one twenty-four-hour period 64.5 gm. of urea. In making several tests, such as those described, the urea with great uniformity rose to from 30 to 35 gm. per day, and if much exercise should have been taken during the final period 35 to 40 gm. were not uncommon.

In making these tests from time to time, other important features were noted. For example, it was noticed almost constantly that, following the test, the patient appeared to be very much improved over his former condition. Most of this improvement was of such a nature that it could not be definitely measured. The patient, however, appeared to be fully aware of the fact, and indefinitely I shared his opinion. For this reason I have made these observations with more or less frequency in each patient for the purpose of obtaining, first, diagnostic and prognostic information; second, for possible therapeutic advantages; and third, that the patient's interest in his case and its management may be intelligently and optimistically maintained.

It is a fair inference that, if known, the output of urea can by simple measures and with safety be so stimulated that from an average of 10 to 15 gm. per day, an amount double this may be uniformly reached; the anatomic alterations and physiologic capacity are such as to eliminate urea, chlorids, phosphates, sulphates, etc., with fair safety. The danger to these chronic interstitial nephritics must, then, lie in the failure of the

kidneys to eliminate other toxic substances of a nature so subtle as so far to defy analysis. It is also probable that the circulatory, and especially the extravascular circulatory changes are responsible for the failure to eliminate these heretofore undefined toxic agents. From this it may be readily seen that such measurements as those described fall far short of our requirements. Nevertheless, they are, taken in connection with such other observations as those of estimating the blood-pressure, the retinal fields and a careful review of the symptomatology, the best obtainable at the present time. As the results of my own observations, I am of the opinion that those cases in which there can be demonstrated, with regularity, a fair or large reserve renal capacity offer the best chances for prolonged life, physical and mental capacity and usefulness, while those in which the reserve renal capacity is but slight are in much greater risk of prematurely encountering the various serious accidents which accompany the later stages of this malady.

On the information obtained may be based some important details of management. In my own practice I advise such active and passive muscular exercises as may be taken without evidences of urea retention. Also the amount of proteid ingestion, always small or moderate, is gauged in like manner. These I consider points of great practical importance.

Along similar lines estimations may be made of the capacity of the kidneys to eliminate urinary water; also of chlorids. The latter, taken in connection with observations on the weight of the patient and of the extra-vascular serum accumulation, blood-pressure and cardiac hypertrophy, is of prime importance and should be made with regularity. It is not my purpose, however, in this paper to consider this line of thought; my main object is to stimulate further and more accurate investigation.

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## ABSTRACT OF DISCUSSION

DR. FRANK BILLINGS, Chicago: What Dr. Wells has read to us this morning should be a lesson; what he has given us has been an individual study of a diseased organ, the kidney, and there is much that is new in it. The method he employs in estimating the functional capacity of the kidney is interesting; perhaps if one wished to offer a criticism one might say that one could not, by such measures as he employed, fully estimate the physiologic function of the kidney, or the metabolism of the body; yet clinically the measure he employs is the only one that is practical by which we can reach any such conclusions. The painstaking way he has worked with the different diets, day after day, and all before he has arrived at any conclusion, shows that his work and study is worthy of careful consideration. He is using the same methods we should use in other diseases, such as diabetes—measuring the individual capacity of the patient.

DR. WALTER L. BIERRING, Des Moines, Iowa: The thought arises whether the disturbances in the nutritive balance may not be influenced by other organs besides the liver. In considering the condition termed chronic nephritis, a very close relationship was recognized between that triad of structures, the myocardium, the blood-vessels and the kidneys. It is also exceedingly difficult to estimate the functional capacity of the kidney, to note only the urinary findings; and oftentimes many of the symptoms which are most indicative of chronic nephritis are those of retention phenomena. The prognosis in chronic nephritis is dependent largely on the condition of the myocardium, and it appears to me that possibly in our efforts to preserve this reserve force referred to in the paper, we really bring about a condition more favorable to the myocardium or myocardial function; whenever we bring about such a condition by means of proper diet or otherwise, it tends to lower arterial pressure, lessen the strain on the heart, the retention phenomena become less marked, and a better functional ability of the kidney is brought about.

DR. EDWARD F. WELLS, Chicago: My paper illustrates the futility of attempting to make a suitable presentation of an important subject in the short time allotted; therefore I limited my remarks mainly to a consideration of certain tests for measuring the reserve capacity in chronic interstitial nephritis, with a well-preserved circulatory balance. In a few words I mentioned the fact that under certain circumstances, especially with a failing circulatory balance and a consequent nutritional disturbance, the tests mentioned are inapplicable. It must be clearly apparent that the tests mentioned are crude, but, rudimentary as they are, the methods are those which I have found available and useful for testing the urinary capacity of my patients. To these there should be added a study of the functional capacity of all the organs engaged in

the preparation for urinary excretion. Those presented I should be pleased to have considered simply as a beginning of work along these lines, with the confident expectation that, intelligently practiced, they will be found as useful in the malady mentioned as are similar procedures in the study and management of diabetics. My object has been to extend our diagnostics—making a therapeutic and a prognostic diagnosis, if you will allo wthe terms; nevertheless, certain beneficial therapeutic results were obtained from the tests employed. However, I do not wish to lay any undue stress on this point.

# PATHOLOGIC FINDINGS IN HYPERTENSION

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During the last ten years much has been written on the subject of blood-pressure and hypertension. Most of the work has been based on clinical findings; comparatively little has been done in the way of following cases to the autopsy table. There are, of course, grave objections to drawing deductions from a comparative study of blood-pressure determinations taken shortly before death and the pathologic lesions found at autopsy. At the same time it seemed that the study of a group of cases which had been followed to the autopsy table might be of interest.

All observers are agreed in regard to the frequent occurrence of hypertension in nephritis. Cushing[1] and others[2, 3] have shown that high blood-pressure occurs in cases with increased intracranial pressure. The chief discussion has been directed toward the question of the occurrence of hypertension in arteriosclerosis independent of a nephritis. Sawada[4] has never seen a case of hypertension over 170 in simple arteriosclerosis. Romberg[5] considers that persistent high blood-pressure in a suspicious case establishes the diagnosis of chronic interstitial nephritis.

1. Cushing, H.: Bull. Johns Hopkins Hosp., 1901, xii, 290.
2. Eyster, Burrows and Essick: Jour. Exper. Med., 1909, xi, 489.
3. Robinson, G. C.: Arch. Int. Med., May, 1910, v, 483.
4. Sawada: Deutsch. med. Wchnschr., 1904, xxx, 425.
5. Romberg: Kong. f. inn. Med., 1904, lx, 17.

The material reported in this paper consists of the pathologic findings in every case showing a systolic blood-pressure of over 160 in life which has come to autopsy from the medical wards at the Massachusetts General Hospital from Jan. 1, 1907, to April 25, 1911. Before 1907 the blood-pressure determinations were not made in sufficient numbers to give adequate data. Since 1907, while blood-pressure determinations have not been used as a routine in every case at the Massachusetts General Hospital, yet it is fair to say that such determinations have been made in nearly every case, if not every case, that would come into the group under discussion.

Unfortunately, only the determinations of the systolic blood-pressure are available. The instrument used has been the Riva-Rocci apparatus with the wide armcuff. The observations were all taken in the recumbent position when the patient was able to lie down. The apparatus was placed on a table practically on a level with the heart, with the arm at the same level. The determinations were made by various individuals, but in general the method was that advocated by Janeway[6] and Sawada[4]; namely, the point at which the first full beat returns after the obliteration of the pulse. Janeway and Park[7] have shown that in clinical blood-pressure determinations, if the wide arm-piece be used and if the return of the first fully developed pulse-wave be taken, even advanced arterial thickening and calcification probably do not intrude an error of any importance.

The limit of 160 was taken, as Janeway[6, 8] and others[9, 10] believe that such a limit is rarely exceeded in normal individuals. From Jan. 1, 1907, to April 25, 1911, there were in the medical wards of the Massachusetts General Hospital fifty-three cases with blood-pressures over 160 that came to autopsy. The hospital

6. Janeway, T. C.: Clinical Studies of Blood-Pressure, New York, 1904, p. 64.
7. Janeway and Park: Arch. Int. Med., Nov. 15, 1910, vi, 586.
8. Janeway, T. C.: Am. Jour. Med. Sc., 1906, i, 772.
9. Osler: System of Medicine, iv, Chap. x, 426, 447.
10. Woley: THE JOURNAL A. M. A., July 9, 1910, p. 121.

admits only acute cases or acute manifestations of chronic cases. Most of the autopsies were done by Dr. Oscar Richardson; a few by Dr. J. H. Wright. The histologic examinations were made by Dr. Wright.

In the discussion of the diagnosis, little attempt has been made to balance the relative importance of the pathologic findings. If a kidney lesion of any description is present, it is considered that such a case belongs to the group of cases of hypertension associated with kidney lesions.

### HYPERTENSION WITH LESIONS IN THE KIDNEYS

The pathologic findings showed some kidney lesion in thirty-eight cases, or over 71 per cent. These thirty-eight cases include one case which was, pathologically, acute degeneration of the kidneys and one case of hydronephrosis. In seven of the thirty-eight cases showing kidney lesions, or 13 per cent. of the whole series, the lesions found at autopsy were essentially confined to the kidneys (Cases 2, 8, 19, 36, 38, 42 and 53). Five of these seven cases showed pathologic changes classified as chronic glomerulonephritis, one as subacute glomerulonephritis and one as chronic interstitial nephritis. The maximum systolic blood-pressure in this group of seven cases ranged from 165 to 240.

### HYPERTENSION WITH ARTERIOSCLEROSIS

Arteriosclerosis was found at autopsy in thirty-seven of the fifty-three cases, or 69 per cent. General arteriosclerosis was associated with lesions in the kidney in twenty-eight cases, or 52 per cent.

There was only one case (Case 46) of hypertension with arteriosclerosis in which there was no kidney lesion, no cerebral lesion and no cardiac lesion, except simple hypertrophy and dilatation, the blood-pressure was 210. This case was in the hospital only twenty-four hours, and there was only one observation of blood-pressure. The patient was in coma. The urine showed no albumin but a slight trace of sugar. The pathologic examination

showed a woman of 60 years, with slight general arteriosclerosis, a heart weighing 520 gm., normal kidneys weighing 268 gm. and no other lesions worthy of note.

In two cases (Cases 41 and 47) of fibrous endocarditis with no lesions in the kidneys, the valvular lesions were slight and the essential pathologic change seemed to be arteriosclerosis.

### HYPERTENSION WITH CEREBRAL LESIONS

In eight of the fifty-three cases, or 15 per cent., there were definite cerebral lesions. One case was associated with a chronic nephritis and three with arteriosclerosis. In four cases no other blood-pressure-raising factor besides the cerebral lesion was apparent.

### HYPERTENSION WITH CARDIAC LESIONS

In thirteen of the fifty-three, or over 24 per cent., there were definite cardiac lesions in addition to simple hypertrophy and dilatation of the heart, and in eleven of these thirteen there was endocarditis of the aortic valve. In every case in which the endocardium was affected, the aortic valve was involved. Three of the thirteen cases showed no other lesions which might be assumed to raise the blood-pressure.

### HYPERTENSION WITHOUT KIDNEY LESIONS

There were fifteen cases, or 28 per cent. of the series, in which no kidney lesions were found; at autopsy seven showed cerebral lesions. In four cases the chief pathologic lesion was cerebral hemorrhage. The blood-pressure varied in these four cases from 175 to 260. In one case (Case 16) the cerebral hemorrhage was traumatic; in that case the blood-pressure was 175. In the other three cases (Cases 21, 22 and 48) the cerebral hemorrhage was apparently due to the rupture of an arteriosclerotic cerebral vessel. In these three cases, the blood-pressures were over 200. In the same group is one case of brain tumor (Case 33) with a blood-pressure of 190; one case of degeneration in the pons (Case 43) with a

blood-pressure of 175, and one case of miliary tuberculosis with a tuberculous meningitis (Case 31) with a blood-pressure of 165. Consequently, in seven out of fifteen cases of hypertension not associated with a lesion in the kidney, there was some cerebral condition which might have caused cerebral pressure. Cushing and others have shown the relation between increased intracranial pressure and an increased blood-pressure.

In this group of fifteen cases of hypertension without kidney lesions, seven showed cardiac lesions. There were two cases (Cases 10 and 44) in which intracardiac thromboses were found without other cardiac lesions beyond simple hypertrophy and dilatation and without arteriosclerosis. There was one case of syphilitic aortitis (Case 25) with a slight amount of fibrous endocarditis of the aortic valve. In addition, one finds in this group four cases (Cases 41, 45, 47 and 52) of fibrous endocarditis of one or more valves of the heart, all associated with arteriosclerosis and one case with primary pernicious anemia. The aortic valve was affected in every case. In the same group of fifteen cases of hypertension without kidney lesions comes the case of arteriosclerosis (Case 46). In this group of fifteen cases of hypertension without lesion in the kidneys there were seven patients under 50 and eight over 50 years. The maximum systolic blood-pressure varied from 165 to 260.

### HYPERTENSION WITHOUT LESIONS IN THE KIDNEYS AND WITHOUT ARTERIOSCLEROSIS

There were seven cases with neither arteriosclerosis nor nephritis. Of these seven cases four showed cerebral lesions. One was a case of brain tumor (Case 33), one was a case of general miliary tuberculosis with tuberculous meningitis (Case 31), one a case of degeneration in the pons and carcinoma of the ovary (Case 43), one a case of cerebral hemorrhage due to trauma (Case 16). The remaining three cases in this group were cardiac cases (Cases 10, 25 and 44). The ages in this group were from 30 to 52. This group of seven cases is char-

acterized by a moderate degree of hypertension as a rule, two showing a maximum systolic blood-pressure of 165, one of 170, two of 175, one of 190 and one of 200. Therefore, in this series of fifty-three cases in the absence of both arteriosclerosis and any lesion in the kidney no blood-pressure over 200 was found.

If one considers only the cases with more than one blood-pressure observation and only cases showing constantly a blood-pressure of 200 or over there were ten cases all of which were cases with kidney lesions. In nine of these ten cases arteriosclerosis was also present, although in two cases the arteriosclerosis was slight.

Of fifty-one cases in which we have the kidney weight twenty-nine, or 56 per cent. +, were distinctly atrophic i. e., weighing under 250 gm. Of the twenty-nine kidneys weighing less than 250 gm. twenty-seven showed kidney lesions and two showed no kidney lesions. One case (Case 31) showed miliary tuberculosis in which the blood-pressure was 165. In this case the kidneys weighed 208 gm. but the heart also was small, weighing 223 gm. The other (Case 48) showed arteriosclerosis and cerebral hemorrhage. The blood-pressure varied between 260 and 125. The heart weight was 335 gm. and the kidneys 190 gm. Only eleven cases of the thirty-seven with kidney lesions, or 27 per cent., failed to show small atrophic kidneys. Of the ten cases with kidney lesions, with kidneys weighing more than 250 gm., five showed kidneys weighing 250 to 300. Histologically, all showed atrophic conditions. In one case, with kidneys weighing 313 gm., the chronic interstitial changes were slight (Case 9). This was the case of lead poisoning and pneumonia. Three of the other four cases were cases of subacute glomerulonephritis and the other was a case of acute glomerulonephritis. In seven of these ten cases the blood-pressure was over 200 mm. of mercury. Marked hypertension occurs in this series in a certain number of cases in association with kidneys which are not atrophic, and in acute and subacute glomerulonephritis.

The weights of the hearts were of considerable interest; of the fifty-one cases in which the heart weights were recorded only thirteen weighed less than 400 gm., ten weighed between 400 and 500, and twenty-nine, or 56 per cent., weighed over 500 gm. Of special interest is Case 48, in which the heart weighed 335 gm. In this case a blood-pressure of 260 was present for twenty-four hours, of 180 the next twenty-four hours, but the pressure sank to 125 on the third day, the day of death. Case 12 was observed for two weeks, with three observations scattered through the period. The blood-pressure varied between 225 and 190. The heart weighed 363 gm. Consequently, a high blood-pressure of over 190 may persist for a period of days with only a very moderately hypertrophied heart.

The anatomic and clinical diagnoses approximately correspond in forty-four of the fifty-three cases. In five cases (7, 9, 27, 49 and 50) kidney lesions were found at autopsy, but were not diagnosed in life. In one of these five cases (Case 9), one of lead poisoning with lobar pneumonia, the kidney lesion was slight. In two cases (7 and 27) the nephritis seemed incidental. In five cases (22, 25, 30, 41 and 46) a kidney lesion was diagnosed but was not found at autopsy. This diagnosis was, apparently, based chiefly on the high blood-pressure.

In these fifty-three cases albumin was absent in only four; in three of these four there was no kidney lesion. In these four cases the clinical diagnosis of nephritis was made twice and in one the kidney lesion was present and in one a kidney lesion was not present at autopsy.

Of the fifty-three subjects thirty-six were males and seventeen females. The males predominate over two to one. In the ten-year periods there were one from 20 to 29, nine from 30 to 39, nineteen from 40 to 49, ten from 50 to 59, nine from 60 to 69, five from 70 to 79 and one subject of unknown age.

The age period of from 40 to 49 has nearly twice as many as any other period. From 40 to 59 are twenty-nine cases, or 54 per cent., of all the cases. The youngest patient was 25, the oldest 73.

## SUMMARY

Some kidney lesion was present at autopsy in over 71 per cent. of the cases of hypertension. In 13 per cent. the kidney lesion was essentially uncomplicated by other possible blood-pressure-raising factors; the lesion in the kidney was atrophic in 72 per cent. of the kidney cases. Hypertension also occurs in the so-called acute and subacute glomerulonephritis as well as in the atrophic form of nephritis. Arteriosclerosis was present in 69 per cent. of the cases, but in only one case could all other lesions which might cause hypertension be excluded.

In fifteen cases no kidney lesion was found at autopsy. Seven of these cases presented cerebral lesions, seven cardiac lesions and one general arteriosclerosis. In every case of valvular disease of the heart, the aortic valve was involved. No patient without either nephritis or arteriosclerosis showed a blood-pressure of over 200. All the patients with repeated and constant blood-pressure readings of over 200 showed some kidney lesion.

In thirty-eight of the fifty-one cases there were definitely hypertrophied hearts, yet in some instances high blood-pressures were observed to persist for days with hearts weighing less than 400 gm.

The following conclusions seem justified:

Hypertension occurs most commonly in association with some lesion in the kidney. The most common lesion is an atrophic kidney with increase of connective tissue and disappearance of glomeruli. Hypertension occurs also in association with acute, subacute and chronic glomerulonephritis.

Hypertension occurs not infrequently in association with cerebral lesions.

A moderate degree of hypertension may occur in cardiac lesions. In valvular cardiac lesions the aortic valve is apparently always involved.

Hypertension may occur rarely in cases of general arteriosclerosis without other lesions.

With a continued systolic blood-pressure of over 200, some form of nephritis is found.

Hypertension usually indicates well-marked cardiac hypertrophy. The hypertrophy may be moderate in connection with a well-marked hypertension over a considerable period.

NOTE.—In addition to the authorities previously cited, the following may be found of interest:

Barker, L. F.: Am. Jour. Med. Sc., 1910, i, 631.
Buttermann: Deutsch. Arch. f. klin. Med., lxiv, 1.
Elliott, A. R.: Am. Jour. Med. Sc., 1910, i, 648; THE JOURNAL A. M. A., April 13, 1907, p. 1247.
Geisböck: Deutsch. Arch. f. klin. Med., lxxxiii, 363.
Goepp: Pennsylvania Med. Jour., April, 1911,
Hasenfeld: Deutsch. Arch. f. klin. Med., lix, 193.
Husch: Deutsch. Arch. f. klin. Med., lxviii, 55 and 331.
Krehl: Deutsch. med. Wchnschr., xxxi, 1872.
Loeb: Deutsch. Arch. f. klin. Med., lxxxv, 349.
Longcope and McClintock: Arch. Int. Med., 1910, vi, 493.
Pal: Gefässkrisen, Leipsic, 1905, i, 275.
Rudolph: Brit. Med. Jour., 1910, xii, 1667.

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## ABSTRACT OF DISCUSSION

DR. WILLIAM OPHÜLS, San Francisco: I was much interested in Dr. Lee's paper, because lately I have been working on the same question, but from an anatomic point of view. I should refer those of you who are interested to the Scientific Exhibit, where some microphotographs and charts are exhibited, which show the result of an investigation of kidneys, heart and blood-vessels in 1,000 consecutive autopsies. As is shown in these charts, general arteriosclerosis and the so-called small granular kidney are closely associated. Glomerulonephritis proper, however, can be distinctly separated from these primarily arteriosclerotic cases.

Dr. Lee's clinical observations bear out very closely what I have seen anatomically. In regard to hypertension I am inclined to place more importance on general arteriosclerosis than on the renal lesions which may be associated. I was quite astonished myself, in looking over my cases, to learn how comparatively insignificant the renal lesions are in producing the symptom-complex. Undoubtedly at present the rôle of the kidneys in its production is greatly exaggerated.

DR. EDWARD F. WELLS, Chicago: There is an art, as well as a science, in the study of blood-pressure, and the art, to be useful, requires practice. He who measures the blood-pressure rarely and in the exceptional case and attempts to draw conclusions from his occasional observations, places himself in the position of one who would form his opinions on the pulse under similar circumstances; both would obtain very indefinite and obscure impressions of the great variations in the characteristics of the blood-pressure and pulse, respectively, and would underestimate the value of the procedure. He, however, who measures the blood-pressure as a diagnostic routine procedure obtains useful and pertinent information.

The blood-pressure which rises gradually through a long period of time and is accompanied by cardiovascular and nephritic morbid changes, is probably fundamental and permanent, and is one which cannot be materially reduced, and it may be questioned whether this should be attempted. There is, however, an exalted blood-pressure which attends certain toxic conditions, as, for example, the toxemia of pregnancy, which results in eclampsia, in which the blood-pressure may rapidly rise to great heights. Although we do not yet know fully the relations of the blood-pressure to the toxic agent in these cases, nevertheless we are justified in regarding it as due to the rapid introduction into the circulating liquids of a powerful toxin which acts with intense energy on the vasomotor nerves. Such high blood-pressures quickly fall on removal of the offending cause; they are clearly functional. Now in the class of cases first alluded to, there may be added to the ordinary high blood-pressure of the individual a more or less rapidly advancing increase in tension, due to some ephemeral toxemia, and which may disappear with celerity when once the extra burden is removed, leaving the blood-pressure at the usual high level for the individual, but the reduction is not materially lower than is habitual for the patient. It is my belief that the recognition of these facts is of practical importance, first, to the patient's welfare, and second, to the fair fame of medicine.

DR. FRANK BILLINGS, Chicago: What has been said regarding cardiovascular changes, agrees with the statement already made that the cardiovascular or vascular changes with the hypertrophy of the heart are very important things to consider in blood-pressures. Sometimes in our ignorance the elevation in the blood-pressure is ascribed to a toxemia; there seems to be nothing else which will describe it. However, toxemia has been recognized in many other conditions in which there is an increase of blood-pressure; some vasomotor process such as is exemplified in the phenomena which appear in hyperthyroidism. In the early stages of this disease there is a blood-pressure of 180 or 200, and this is before the disease has progressed to changes in the cardiovascular system. This

must be the result of a toxemia, something which produces overfull blood-vessels. As Dr. Wells stated in relation to the management of such conditions, the existence of a permanent blood-pressure is in a sense conservative; it is Nature's method.

We must consider hydrostatic pressure, but there is another condition, toxemia, which we must not neglect. I agree with Dr. Lee that there are many other things that cause hypertension, such as cardiovascular changes and other changes referable to the kidney. I have watched many cases in the clinics, many that have gone to autopsy; I have seen patients suffering from toxemia without apparently any cardiovascular changes; but at autopsy the kidneys were found to be practically worthless, or functionless.

Just one other word. I do not believe that we can say definitely that there is an exact dividing line between the pathologic and the normal in these cases. To say that 160 is the limit of health, or the point at which disease begins, I think is wrong. There are people of the very nervous type who, under certain conditions, such as overwork, worry, and the like, run up the point to 160, 170 or 180, even, and here we find associated the toxemia that goes with fatigue. When these people are treated with ordinary hygienic measures there is a lessening in the blood-pressure. I do not believe that we have any right to have a statement go forth that a blood-pressure of 160 or more really means, necessarily, disease.

DR. C. F. HOOVER, Cleveland: For the past few years I have studied the diastolic arterial pressure in all suspected cases of hyperthyroidism and I have yet to find a patient in whom there is an elevation of the diastolic pressure even when the systolic pressure is high. My attention was attracted to this point by cases with cardiovascular disease being referred to the surgical wards for operation on goiter which these patients happened to have. The goiters in such cases were merely incidental and were not the cause of the cardiac symptoms.

DR. CHARLES L. GREENE, St. Paul, Minn.: With respect to the findings in these cases of aortic lesions, in the cases that have been so ably described by the reader of the paper, if the cases were in fact aortic regurgitation, then what has been presented should not be included among the high-pressure cases. The experience of all of us who are doing this sort of work shows that we may get a very high systolic pressure, but for different reasons, as described by Dr. Hoover. With the Corrigan pulse we may find a high systolic pressure and a very low diastolic pressure.

DR. WALTER L. BIERRING, Des Moines, Iowa: I should like to ask the reader of the paper if any histologic examination of the brachial artery was made and compared with the condition of the other arteries in the body. It has become recog-

nized that marked differences often exist in the pressure in the brachial and the femoral arteries, and it would be interesting to know if local changes in the blood-vessels could account for this difference.

In determining arterial pressure by the simpler method of palpation, it has also seemed to me far more satisfactory to palpate the femoral artery rather than the radial or the brachial, and by comparative tests one can make much closer estimates in this way with the findings of different forms of special apparatus used for this purpose.

DR. ROGER I. LEE, Boston: Only a macroscopic examination of the adrenals was made in these cases. No gross lesions were found.

Among these cases was one of syphilitic aortitis. The spirochetes were found in the walls of the aorta. Two or three other patients gave a history of syphilis.

Only rarely were histologic examinations of the blood-vessels made. The brachial artery was the one used, as a rule to ascertain the blood-pressure. The femoral artery was occasionally employed, but merely as a control for the brachial artery. But in the synopsis the conclusions were drawn from the results obtained from the brachial artery.

I agree with Dr. Billings in regard to setting a limit, or trying to set a limit between what is pathologic and what is normal; the limit of 160 was merely taken because we wanted some limit and 160 is generally regarded as being a fairly good dividing line. It is evident that the diastolic blood-pressure may be very variable in these cases; a further study will result, no doubt, in more satisfactory conclusions.

The cases studied include only one case of frank aortic regurgitation, and one case of aortic stenosis.

The primary purpose of my paper was to find out how great a rôle arteriosclerosis played in hypertension, inasmuch as the German schools have insisted on the close relation between hypertension and kidney lesions. It should be remembered that kidney lesions, however slight, may be sufficient to cause a high blood-pressure. It is certainly very difficult to balance the relative importance of the different lesions. One must think of the so-called latent nephritis, a name applied by the Germans. In this study I classified all cases having any kidney lesions under the head of hypertension associated with kidney lesions.

Another reason for my undertaking this study was that I wished to place hypertension on an anatomic basis so far as possible. While as yet few cases of hypertension have been recorded as the result of a toxemia, it is certain that soon many will be. Barker has reported a case of transitory high blood-pressure in a case of tabes with gastric crises. These cases must be carefully studied, especially in regard to the condition of the heart, kidneys and blood-vessels.

# THE INCIDENCE OF SEROFIBRINOUS PLEURISY AND EMPYEMA AS COMPLICATIONS AND SEQUELÆ OF PNEUMONIA, WITH REMARKS ON THEIR MEDICAL TREATMENT

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It is admittedly desirable that the guess methods relating to the incidence of both serofibrinous pleurisy and empyema as complications and sequelæ of pneumonia should give way at the earliest possible moment to exact knowledge. It has been the current professional impression that pleurisy is the most common complication of the pneumonic process, but it must be confessed that there is no available statistical evidence to confirm it fully. Again, the precise definition of the term empyema is free from difficulty, it being applicable to a collection of pus in the pleura, however small, while that of serofibrinous pleurisy secondary to pneumonia is distinctly difficult.

In our view, pleurisy in the clinical sense should be regarded as a complication when it co-exists, either as a severe form of the dry plastic variety with marked friction to auscultation or accompanied by sufficient effusion to be demonstrable by means of the physical signs. On the contrary, the slight dry pleurisy which is ordinarily associated with pneumonia is to be looked on as a part of the usual pathologic picture of the disease.

In all cases in which a pleural exudate is obtainable, an etiologic distinction between the recognized varieties

is to be based alone on a bacteriologic examination. In the case of empyema, more particularly when it occurs in children, it may happen that the area of lung-consolidation is small, hence effectually cloaked by the secondary empyemic process. Unless a bacteriologic study is made of all pleural exudates, the cases last described would fail to be recognized as being of pneumococcic or secondary origin.

In general, it may be authoritatively stated that serofibrinous pleurisy is of more frequent occurrence than empyema in lobar pneumonia, a dictum strongly supported by the present statistical inquiries, as will be seen hereafter. It has been found that ante-mortem observations show a smaller percentage of complicating fibrinous and serofibrinous pleurisies relatively than post-mortem figures, for the apparent reason that the lighter graded of these varieties escape observation during the life of the patient. In the case of empyema, however, this discrepancy would appear to be less marked.

A post-mortem examination has frequently revealed an associated pleuritis entirely unsuspected, since this complication often has an insidious onset without either the usual "stitch-like" pain in the involved side or showing any effect on other phenomena belonging to the primary disease. The physical signs, although well-known, merit extended and careful investigation and, should doubt remain as to the diagnosis of complicating pleurisy, an exploratory puncture should be undertaken without delay. It is particularly true of the pleuritis which is secondary to pneumonia in children that while the withdrawn fluid may be serous at first, it soon becomes purulent. The transition, however, is not to be ascribed to a secondary invader but to the action of the pneumococcus.

The statistical observations which form the basis of the present paper embraced an examination of 68,982 clinical and post-mortem records, from which we culled

2,512 cases of pneumonia and found that of these, 1,335 presented complications. In the 2,512 cases of pneumonia, serofibrinous pleurisy occurred in 198 and empyema in 68.

A total of 68,520 clinical case reports, exclusive of 462 post-mortem records, for which no clinical notes could be found, were carefully scrutinized with the following result: Total number of cases of pneumonia, 2,050, in which 890 presented complications and of which 128 were instances of serofibrinous pleurisy and 41 of empyema.

The large number of cases of pleural effusion associated with pneumonia, or 169, in which the date of onset could be determined, promised us the opportunity we desired to determine the relative frequency of the different forms of pleurisy, both during the course of pneumonia and as sequelæ. It was necessary to discard a small proportion in which the notes, especially with relation to time of occurrence of the crisis, were imperfect or failed to show the day of onset of the pleuritis. It is not claiming too much to state that it was necessary to lavish extreme care and patience on the work of scrutinizing the histories in order to determine the date on which the pleurisy or empyema in question in each individual case commenced.

We found that of the 128 cases of serofibrinous pleurisy, 106 occurred as complications and twenty-two as sequelæ, while of the forty-one cases of empyema, twenty-four were classed as complications and seventeen as sequelæ. These figures indicate that serofibrinous pleurisy occurs in 5.12 per cent. as a complication and 1.07 per cent. as a sequel of pneumonia. Serofibrinous pleurisy as indicated by these collective investigations is of much more frequent occurrence secondary to lobar pneumonia than empyema, the ratio being 3 to 1 in favor of the former condition. Empyema occurred in forty-one out of 2,050 cases, or 2 per cent., and it will be observed somewhat more frequently as a complication than as a sequel.

Considering a total of 462 cases of pneumonia occurring at the Philadelphia Hospital, in which the autopsy records alone were consulted, we found that complications were mentioned in 445 instances, of which eighty-eight or 19 per cent., were pleurisy with effusion, e. g., seventy cases of serofibrinous character and eighteen of purulent character.

An analysis of 858 cases from the same institution, in which the clinical records were also scrutinized, showed complications in 404 cases, of which only thirty-nine were instances of pleural effusion. Of the latter, in thirty-four the exudate was serofibrinous, and in five, purulent. Among the thirty-four cases of serofibrinous pleurisy, twenty-five were classed as complications and nine as sequelæ, while all of the empyemas were complications, i. e., occurring before the crisis.

The total number of records examined at the Protestant Episcopal Hospital (see table) were 1,085. Of these, 464 showed complications, of which 124 were pleurisies, ninety-one serofibrinous and thirty-three purulent. Of the serofibrinous form, seventy-eight were complications and thirteen sequelæ, while of the thirty-three purulent, eighteen were complications and fifteen sequelæ.

The accompanying table will enable the reader to make a ready comparison between the figures obtained from the different institutions, which are there represented; and it also reveals at a glance the total number of records consulted, the number of cases of pneumonia from all sources, the number of instances in which complications were mentioned and the relative number of cases in which serofibrinous and purulent pleurisy, both as complications and sequelæ, occurred.

The figures of Musser and Norris[1] showing the results of their collective investigations, based on clinical observations, are quite in harmony with those given above. Thus, out of a total of 24,511 cases, studied by

1. Osler: Modern Medicine, ii, 597.

| Name of Hospital | Records Consulted | Total number of pneumonias | Complications mentioned | Serofibrinous | | Purulent | |
|---|---|---|---|---|---|---|---|
| | | | | Complications | Sequelæ | Complications | Sequelæ |
| Philadelphia General .... | 41,377 | 858 | 404 | 25 (2.9%) | 9 (1.05%) | 5 (0.58%) | 0 ..... |
| Protestant Episcopal ..... | 24,795 | 1,085 | 464 | 78 (7.19%) | 13 (1.2%) | 18 (1.66%) | 15 (1.38%) |
| Medico-Chirurgical ..... (Recent records) | 2,348 | 107 | 22 | 3 (0.28%) | 0 ..... | 1 (0.093%) | 2 (0.196%) |
| Total ..... | 68,520 | 2,050 | 890 | 106 (5.12%) | 22 (1.07%) | 24 (1.17%) | 17 (0.83%) |

them, pleural effusion occurred in 1,535, or 6.26 per cent. On the other hand, the collected cases from autopsy records by these observers are at variance with our own results. For example, they found pleural effusion in 405 out of 974 necropsy records, or 41.58 per cent., while we found in 462 autopsy reports of pneumonia occurring at the Philadelphia Hospital (see above) only eighty-eight instances of pleural effusion, or 19 per cent.

Thomas McCrae stated in a personal communication that out of twenty-nine cases of empyema secondary to lobar pneumonia, twenty-five were classed as complications and only four as sequelæ. These figures indicate a much larger preponderance of empyemata occurring as complications in pneumonia than as sequelæ, thus differing from the results of our collective investigations, e. g., in a total of forty-one cases, twenty-four developed prior to the occurrence of the crisis and seventeen were distinctly postcritical.

### TREATMENT

In non-pneumococcic pleurisy of the serofibrinous variety, it is the custom of many clinicians to aspirate early, and we believe that the disease has in the past been too conservatively treated. When we are dealing with either serofibrinous pleuritis or empyema occurring secondary to pneumonia, however, an expectant method, unless thoracentesis be urgently needed, is to be adopted until the crisis has been passed, but if the latter fail to appear at the proper time, then the exudate should be promptly withdrawn. On the other hand, if a critical decline of temperature takes place in due season, a serofibrinous effusion is quickly absorbed in some cases at least, but if not, then recovery must be enhanced by puncture followed by aspiration.

If a massive effusion develop during the fastigium of pneumonia, displacing the heart and other adjacent organs, or if under these circumstances signs of involve-

ment of the non-affected side, such as moist râles, broncho-vesicular breathing and impaired resonance arise, and finally, serious symptoms such as urgent dyspnea or syncopal attacks with cyanosis manifest themselves, the withdrawal of the exudate is to be advised. Such cases, however, may demand more radical operative measures for their cure after the usual crisis, and these should not be too long withheld. Aspiration during the fastigium is a procedure calculated to do harm on account of the slight shock induced by it, hence it should be undertaken only in cases presenting large pleural collections which give rise to the untoward effects already stated.

We desire to state with emphasis that our results from aspiration for pleural effusion in pneumonia prior to the crisis, in patients that have been desperately ill, have been decidedly discouraging.

The aim in the treatment of individual cases of pneumonia in which pleurisy in one of its different forms is associated, is to secure the largest possible degree of comfort to the patient and the withdrawal of the exudate, if it should occur, at the earliest moment compatible with safety to life.

The indications for the use of medicinal substances in complicating pleurisy are few, and nothing in the nature of a depressant, especially such as the coal tar products, is permissible since pneumonia, the primary disease, debilitates every organ of the body, notably the heart. To be avoided also, therefore, are the salicylates, although these as well as quinin and opium exercise a more or less favorable effect in serous pleuritis in general. Opium is also open to objection in the more advanced stages of pneumonia, especially should the bronchi contain secretory products, since the drug exerts a drying effect, thus hindering their dislodgment. A pneumococcus pleuritis may develop and accompany the pneumonic process from the beginning in which case opium may have great usefulness as a therapeutic

agent in the earlier stages, relieving the pain and inducing repose.

Experience dictates that quinin has a beneficial influence on inflamed serous membranes, and it possesses a limited value at least, in the pleuritis of pneumonia, both as a supportive agent and in mitigating the intensity of the inflammatory process. It may be administered in 4 gr. doses in capsule, followed immediately by a few drops of dilute hydrochloric acid to insure its prompt solution, four times daily.

### LOCAL MEASURES

In cases of pneumonia in which severe pains due to associated pleuritis develop early, fixation of the affected area by means of strips of adhesive plaster is an effective and feasible measure. These should be, however, removed in the event of the occurrence of effusion. The use of morphin in small doses, administered hypodermically, is not objectionable during the earlier stages of pneumonia, if demanded for the relief of intense pains that remain unrelieved by immobilization of the side involved. On the other hand, in light grades of associated pleurisy, counter-irritation by means of sinapisms is to be advised. In the adult, if the patient's nervous system be not too sensitively organized, cold applied in the form of an ice-bag or ice-water bag, or better still cold compresses reapplied at least every hour, as suggested by Baruch, with the least possible disturbance to the patient, is a remedy of choice.

We are quite convinced of the extreme importance of affording prompt relief of the pain, so as to enable the function of respiration to be carried on the more actively, and thus also to preserve the nervous tone and equilibrium of the patient.

In concluding, our best thanks are due to Drs. H. Leon Jameson, Harry W. Bauer and Ernest E. Laubaugh, for material assistance in collecting the statistical data presented above.

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## ABSTRACT OF DISCUSSION

DR. J. N. HALL, Denver: I wish to comment on a series of sixty-two cases of empyema seen in my private and consultation practice in the past nine years, with a view of urging the necessity of earlier diagnosis. I have to thank my assistant, Dr. T. R. Love, for compiling this brief record. Many of these cases were seen weeks or months after the beginning of the disease, and no less than thirteen of them ruptured through the lung. That is, of course, explained by the fact that in the simple and easily recognized cases operations were done at home, while in many of the obscure the patients came far, often from other states, for investigation. Twenty-two of the sixty-two patients died—a frightful mortality, and far higher than the average, because of the character of the material. Thirty-four of these cases followed an acute pneumonia; eight were found to be tuberculous patients, often originating, doubtless, in pneumothorax; five were associated with bronchopneumonia; three succeeded a simple pleural effusion; three followed an ascending infection from appendicitis; two occurred in cases of measles; two after injury to the chest; while one case was found in association with each of the following conditions: General sepsis; perforation of an infected gallbladder in typhoid fever; gangrene of the lung; sarcoma of the pleura; lipoma of the pleura (no exact cause was determined in the latter two cases). Twenty-nine of the cases were right-sided, thirty were left-sided, while three were not noted. There were forty-four males and but eighteen females.

The earlier and freer use of the exploring needle should prevent such humiliation as we must all feel over such a mortality rate as that quoted, and over such a number of perforations through the bronchi. No case should be allowed to drift with fever and obscure chest symptoms without well-considered and applied exploration. I have finally found pus at the thirteenth puncture under anesthesia in a case in which previous less persistent investigation had failed to reveal it, and the man is well to-day. Yet certain cases of empyema deep in the chest, either between the lobes or on the diaphragm, may go on to rupture or death without such external signs as to lead to their detention even by fairly expert clinicians. Such instances should, however, be rare. I wish to reiterate the importance of more persistent attempts to find the pus in cases of obscure chest disease, with fever and leukocytosis, and to urge the danger underlying the diagnosis of "unresolved pneumonia," "thickened pleura," etc. If not cleared up by one or two punctures, it is better, if we can be reasonably certain that pus is present somewhere in the chest, to give an anesthetic with everything prepared for operation and systematically explore the chest until pus is found. The drainage by the surgeon is often a far less formidable procedure than the finding of the purulent focus. We have from 15 to 20 per cent. of the total population of Denver who have come to us because

of some form of disease; many of them have some changes in the chest such as an empyema, or the results of perforation, or lung abscess. I have seen a general streptococci infection resulting from the injection of some sort of a vaccine. It was afterwards learned that the needle was stuck into the lung; as a result an empyema developed and the patient died. As to any damage to the lung itself by exploration, I have never seen serious trouble.

DR. EVERETT J. BROWN, Decatur, Ill.: I think there is one crime which we can frequently hold against the general practitioner and that is the failure to recognize fluid in the chest. In consultation work in a country district I find many cases of empyema and other pleuritic exudates unrecognized. I recently saw a case of empyema in a young man, age 16 years, in which the amount of pus was so enormous as to cause actual deformity from the bulging of that side of the chest. I removed 7 pints by aspiration on one day and three days later 8 pints more were removed by drainage. The patient made a good recovery. I recently had two cases of empyema occur simultaneously in the same family; both were young men. The first case followed pneumonia, and the second boy became infected from the first case by blowing through the tubes attached to a James bottle which the first patient was using to expand the lung; pneumonia with empyema which required drainage occurred. Both patients recovered.

DR. C. F. HOOVER, Cleveland: A very good practice in examining patients with suspected disease of the pleuræ is to auscultate with the unaided ear. If this practice is adhered to it will be found that every accumulation of fluid in the pleural cavity causes an elevation of pitch of the murmur of inspiration and expiration. The sound may be faint or at times inaudible on account of thickening of the pleuræ, but when the respiratory sounds are audible they are heightened in pitch by the presence of fluid whether it is pus, blood or serum.

DR. A. C. MORGAN, Philadelphia: The discussion, it seems to me, has resolved itself into a study of the physical signs. It has, however, been immensely profitable. In the paper presented there were without any doubt many sins of omission as well as of commission; these may occur in attempts at making a diagnosis of a pleuritic exudate, no matter of what type, and may occur through carelessness or through ignorance, or through an improper interpretation of what is found in the physical examination of the chest. In teaching physical signs in the chest to students I have found that it is very hard to get them to study those that are normal; but they are always very eager to study the signs that are abnormal. Place a student to examine a normal chest and he soon assumes an air of satiety; he turns from it and it is very hard to keep his attention. But when given a chest to examine that is abnormal he is delighted and listens to what can be heard, although

he is not fitted to interpret properly what he finds. I think, too, that general practitioners have this same fault; they will not study the normal conditions found in the chest; they do not maintain in their minds what is real and what is abnormal. The best way, I believe, to teach what is abnormal is first to insist on the students being taught what is the normal. They should be made to learn what is the normal; they should be made to become familiar with the normal conditions. If you can satisfy yourself that you know what is normal, then when you strike something that is abnormal, your interest will be aroused, and you will proceed to study the case along definite and concrete lines. I wish to make a plea that we get back of this and learn first the normal; then when we find something that is not normal we shall be in a better position to study our cases intelligently.

# TREATMENT OF DIABETES MELLITUS

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It is impossible in a paper of this kind to consider more than the most important points in the treatment of diabetes mellitus. The various special treatments that have been recommended for this condition cannot be discussed. A bibliography will be appended, but no attempt will be made to give any extended references to the many excellent papers that have appeared on the subject. The object of this paper is to call attention to certain well-defined principles which must govern the treatment of this serious and stubborn disease, if any satisfactory outcome is to be hoped for.

While this paper deals only with the treatment of diabetes, it is necessary for purpose of clearness to refer briefly to the etiology of the disease. A small percentage of cases are caused by some severe pre-existing pathologic condition that removes them from consideration in a paper of this kind. Such cases are those due to carcinoma of the pancreas, to syphilis, etc.

The cases that will be considered in this paper and which make up approximately 90 per cent. of all those exhibited by the patients that present themselves, are due to what may be called errors of metabolism. To assign this as a cause, however, is not to explain, for there are causes operating behind these metabolic errors. A careful study of the habits of a large number of diabetics convinces me that one of the most fertile causes of diabetes mellitus is a long-continued toxemia or autointoxication due to gross errors in eating. There are, of

course, other causes: oft-repeated emotional excitement, the excessive use of starches or of alcohol, arteriosclerosis, that undefinable something which, for want of a better name, we call the gouty diathesis; heredity, sometimes associated with exophthalmic goiter—all these seem to play a part in the etiology of this disease; but by far the most important cause is the one first given, errors in diet.

### WHAT CONSTITUTES A CURE

It should be impressed on the patient that a "cure" of this disease is not possible in the sense in which he understands a "cure," viz., that after the glycosuria has been overcome he may go back to his old habits of diet. He should be told that after his apparent recovery, continued care in eating is essential to his continued health. As well might a consumptive in whom the tuberculous process has been arrested by careful treatment expect to go back to foul air, insufficient light and lack of nourishing food and remain well, as a diabetic to keep his urine sugar-free while violating the very dietetic rules the disregard of which brought on his trouble.

### DIETETIC ERRORS A FREQUENT CAUSE

In the past twenty years I have treated somewhat over 1,100 diabetic patients. A careful study of these cases has impressed me with the fact that the great majority of patients who suffer with this disease do so because, through ignorance, they have grossly abused their systems with the quantity, quality and kind of food used. Too much food, bolting the food so as to preclude proper insalivation, reading, thinking deeply or worrying while eating, using uncooked or but partly cooked starches—all these are contributory causes to that deranged metabolism which exhibits itself as diabetes. Particular stress should be laid on the viciousness of the prevalent habit of using large quantities of carbohydrate foods in which the starches are practically in an uncooked state, baking-powder biscuits, batter cakes, corn-bread, waffles,

various forms of crackers—especially the Graham cracker, so largely eaten under the mistaken idea that it has an extraordinary food value—all these forms of starchy food are bad and contribute in no small degree to recruit the increasing army of diabetes. These causes will be taken up in greater detail as the treatment of the disease is considered.

The value of any treatment for any disease must be judged by results. And the results must have been obtained not in a few isolated cases but in a long series of cases. In order to make clear whether the treatment about to be described is worthy of consideration a table is appended of the cases of all the patients treated from May 1 to Dec. 1, 1910, giving the age of the patient, the duration and severity of the disease and the result of the treatment.

This table, of course, is but the briefest of outlines and is intended only to emphasize the results of the treatment. While more or less complete histories of more than 1,100 cases could be given, such a tabulation would be out of place in a paper of this kind. Before closing, a typical case-history will be given in detail with the treatment.

### OBJECTIVE POINTS IN TREATMENT

In treating the class of diabetics with which this paper deals there are four objects to be kept in view:

1. To free as nearly as possible the blood and other tissues from sugar; to do this it is necessary—

2. To find the individual patient's tolerance for carbohydrate and if possible to increase that tolerance;

3. To find a diet that will furnish the necessary calories without, at the same time, increasing the sugar intake; and

4. To prevent, by dietetic or other measures, the constipation with which the majority of these patients suffer and which increases the toxemic condition.

The first thing to impress on the patient is the fact that this disease—in the class of cases under considera-

tion—is one that possibly has been years in developing and that it is useless and hopeless for him to expect to obtain any relief in a short time. The changes which a long-outraged system has undergone are such as cannot be remedied in a week or a month. In diabetes, more than in almost any other disease (unless it is tuberculosis), the help and cooperation of the patient is absolutely essential to successful treatment.

### FUTILITY OF DRUGS

Another fact to be emphasized is the futility of drugs in the treatment of this disease; futile, because harmful habits cannot be cured by drugs. A large percentage of the patients who present themselves bring with them their bottles of codein and that worse than useless nostrum, Arsenauro. It is an unfortunate fact that many physicians still seem to harbor the belief that arsenic when prescribed under a proprietary name possesses virtues not to be found in the official preparations and, moreover, that it has lost the dangerous qualities inherent in it. I have seen so many patients with the codein habit and aggravated cases of constipation superimposed on the diabetes, and so many with wrecked digestive systems due to the long continued use of Arsenauro and other arsenic solutions, that I must utter a word of warning against the use of these drugs.

Too much stress cannot be laid on this point. Codein and arsenic may have their uses in a limited number of cases, but in the great majority of cases they should be left severely alone. If these drugs were merely worthless, there might not be any serious objections to their use, but they are a positive detriment and their continued use lessens the patient's chances of recovery. Not only that, but whenever a drug is given to a diabetic he is usually less careful in his method of living than if he realizes that his recovery depends on diet and hygiene alone.

PATIENTS TREATED FROM MAY 1 TO DECEMBER 1, 1910

| Sex. | Patient. | Age. | Duration of Disease in Months. | Complications. | Sp. Gr. Urine before Treat. | Duration Treatment in Weeks. | Sp. Gr. Urine after Treat. | Condition at End of Treatment. | Report 1/6/11 |
|---|---|---|---|---|---|---|---|---|---|
| F. | H. A..... | 27 | 5 | ..... | 1.032 | 4 | 1.016 | No sugar..... | No report. |
| F. | W. H. A... | 36 | 27 | ..... | 1.040 | 6 | 1.018 | Trace sugar... | Died 4/11. |
| F. | J. A..... | 62 | 24 | ..... | 1.036 | 7 | 1.014 | No sugar..... | No sugar. |
| F. | G. A..... | 34 | 3 | ..... | 1.030 | 5 | 1.015 | No sugar..... | Trace sugar. |
| M. | F. A..... | 51 | 24 | Diabetic cataract..... | 1.045 | 7 | 1.016 | No sugar..... | No sugar. |
| F. | H. B..... | 38 | 7 | ..... | 1.042 | 5 | 1.016 | No sugar..... | No report. |
| M. | F. W. B.. | 40 | 6 | ..... | 1.038 | 4 | 1.013 | No sugar..... | No sugar. |
| F. | F. B..... | 32 | 2 | ..... | 1.035 | 2 | 1.017 | Transitory case | |
| M. | A. S. B... | 65 | 5 | Arteriosclerosis ..... | 1.030 | 6 | 1.018 | No sugar..... | No report. |
| F. | L. B..... | 69 | 18 | Arteriosclerosis ..... | 1.028 | 3 | 1.016 | Trace sugar... | No sugar. |
| M. | B. M. B... | 41 | 11 | ..... | 1.038 | 5 | 1.014 | No sugar..... | No sugar. |
| M. | S. J. B.... | 63 | 16 | Arteriosclerosis ..... | 1.026 | 2 | 1.016 | No sugar..... | No sugar. |
| M. | D. B..... | 54 | 20 | Pulmonary tuberculosis.. | 1.040 | 7 | 1.018 | Trace sugar... | Died 1/18/11. |
| M. | H. B..... | 57 | 9 | ..... | 1.036 | 8 | 1.015 | No sugar..... | Trace sugar. |
| F. | E. B..... | 68 | 60 | Arteriosclerosis ..... | 1.030 | 4 | 1.012 | No sugar..... | 3% sugar. |
| F. | L. B..... | 56 | 14 | ..... | 1.028 | 3 | 1.014 | No sugar..... | No report. |
| M. | L. B..... | 17 | 6 | ..... | 1.042 | 9 | 1.017 | No sugar..... | Died 3/11, septicemia. |
| F. | S. M. B... | 56 | 24 | Gangrene toe ..... | 1.040 | 4 | 1.016 | No sugar..... | No sugar. |
| M. | L. B..... | 14 | 5 | ..... | 1.045 | 12 | 1.015 | No sugar..... | No sugar. |
| M. | H. C..... | 41 | 4 | ..... | 1.036 | 3 | 1.014 | No sugar..... | No sugar. |
| M. | A. C..... | 54 | 17 | ..... | 1.028 | 5 | 1.015 | No sugar..... | No report. |
| M. | C. W. C.. | 49 | 22 | Pulmonary tuberculosis.. | 1.034 | 7 | 1.018 | Trace sugar... | No report. |
| M. | S. C..... | 45 | 27 | ..... | 1.045 | 8 | 1.012 | No sugar..... | No sugar. |
| F. | M. C..... | 67 | 14 | Arteriosclerosis ..... | 1.042 | 4 | 1.012 | No sugar..... | Trace sugar. |
| M. | R. L. C... | 24 | 7 | ..... | 1.040 | 7 | 1.016 | No sugar..... | No report. |
| M. | M. C..... | 44 | 15 | ..... | 1.036 | 3 | 1.012 | No sugar..... | No sugar. |
| F. | H. C..... | 47 | 20 | ..... | 1.034 | 4 | 1.016 | No sugar..... | No sugar. |
| M. | A. C..... | 44 | 7 | ..... | 1.038 | 3 | 1.014 | No sugar..... | Trace sugar. |
| M. | W. H. D.. | 54 | 11 | ..... | 1.041 | 5 | 1.016 | No sugar..... | No sugar. |
| M. | F. D..... | 14 | 13 | ..... | 1.048 | 6 | 1.015 | No sugar..... | 3% sugar. |
| M. | L. D..... | 36 | 5 | ..... | 1.037 | 6 | 1.016 | No sugar..... | Trace sugar. |
| F. | B. F..... | 19 | 4 | ..... | 1.048 | 7 | 1.014 | No sugar..... | No sugar. |
| F. | H. F..... | 47 | 14 | ..... | 1.036 | 5 | 1.016 | No sugar..... | No report. |
| F. | C. F..... | 50 | 9 | ..... | 1.034 | 4 | 1.018 | No sugar..... | No sugar. |
| M. | J. F..... | 47 | 11 | ..... | 1.028 | 3 | 1.016 | No sugar..... | No report. |
| M. | G. E. F... | 30 | 4 | ..... | 1.032 | 2 | 1.017 | Trace sugar... | No report. |
| M. | W. G..... | 59 | 13 | ..... | 1.038 | 3 | 1.014 | No sugar..... | No sugar. |
| M. | D. G..... | 40 | 5 | ..... | 1.041 | 6 | 1.015 | No sugar..... | No sugar. |
| F. | I. G..... | 44 | 11 | ..... | 1.038 | 5 | 1.017 | No sugar..... | No sugar. |
| F. | G. G..... | 47 | 14 | ..... | 1.040 | 4 | 1.016 | No sugar..... | No report. |
| F. | W. G..... | 48 | 8 | Carbuncle neck ..... | 1.047 | 7 | 1.015 | No sugar..... | 1% sugar. |
| F. | J. G..... | 44 | 7 | ..... | 1.036 | 4 | 1.018 | Trace sugar... | No report. |
| M. | W. H..... | 54 | 14 | ..... | 1.028 | 6 | 1.016 | No sugar..... | No sugar. |
| F. | J. J..... | 58 | 48 | ..... | 1.040 | 4 | 1.016 | No sugar..... | No report. |
| M. | S. K..... | 80 | 5 | ..... | 1.047 | 6 | 1.015 | No sugar..... | 1% sugar. |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| F. | G. K..... | 44 | 11 | ..... | 1.034 | 3 | 1.014 | No sugar..... | No sugar. |
| F. | C. L. K... | 16 | 7 | ..... | 1.046 | 10 | 1.015 | No sugar..... | No sugar. |
| M. | G. M. K... | 82 | 9 | ..... | 1.040 | 7 | 1.016 | No sugar..... | No report. |
| F. | L. L..... | 56 | 24 | ..... | 1.038 | 6 | 1.014 | No sugar..... | No sugar. |
| F. | K. M..... | 49 | 12 | ..... | 1.034 | 3 | 1.012 | No sugar..... | No sugar. |
| F. | C. M..... | 54 | 14 | ..... | 1.036 | 4 | 1.014 | No sugar..... | 1% sugar. |
| F. | K. M..... | 56 | 7 | ..... | 1.034 | 2 | 1.016 | Trace sugar... | 1% sugar. |
| M. | L. M..... | 36 | 11 | ..... | 1.040 | 5 | 1.017 | No sugar..... | No sugar. |
| F. | S. M..... | 59 | 18 | Arteriosclerosis ..... | 1.044 | 7 | 1.017 | No sugar..... | No report. |
| M. | J. Mc..... | 48 | 14 | ..... | 1.046 | 5 | 1.015 | No sugar..... | No sugar. |
| F. | G. M..... | 53 | 20 | ..... | 1.038 | 4 | 1.012 | No sugar..... | No sugar. |
| M. | L. M..... | 39 | 15 | ..... | 1.038 | 5 | 1.016 | No sugar..... | No sugar. |
| M. | J. McN.... | 49 | 15 | ..... | 1.047 | 4 | 1.014 | No sugar..... | 1% sugar. |
| M. | Dr. McG... | 66 | 12 | Arteriosclerosis ..... | 1.044 | 6 | 1.012 | No sugar..... | No sugar. |
| M. | C. N..... | 45 | 8 | ..... | 1.046 | 10 | 1.014 | No sugar..... | No sugar. |
| M. | H. J. M... | 48 | 11 | ..... | 1.040 | 3 | 1.014 | No sugar..... | Died coma. 3/11. |
| M. | D. N..... | 28 | 4 | ..... | 1.044 | 8 | 1.014 | No sugar..... | No sugar. |
| M. | F. R. N... | 47 | 14 | ..... | 1.046 | 4 | 1.014 | No sugar..... | No sugar. |
| F. | H. P..... | 48 | 19 | ..... | 1.038 | 5 | 1.014 | No sugar..... | 2% sugar. |
| F. | J. R..... | 49 | 11 | Gangrene toe ..... | 1.042 | 7 | 1.016 | No sugar..... | No report. |
| M. | H. R..... | 66 | 7 | Arteriosclerosis ..... | 1.036 | 5 | 1.012 | No sugar..... | Died, 1/11. |
| F. | A. R..... | 46 | 15 | ..... | 1.040 | 4 | 1.014 | No sugar..... | No sugar. |
| M. | T. R..... | 57 | 18 | ..... | 1.030 | 3 | 1.014 | No sugar..... | Trace sugar. |
| M. | N. S..... | 55 | 16 | Dim sight ..... | 1.036 | 4 | 1.012 | No sugar..... | No sugar. |
| M. | F. S..... | 24 | 9 | ..... | 1.044 | 5 | 1.016 | No sugar..... | No sugar. |
| F. | L. B. S.... | 63 | 24 | Arteriosclerosis ..... | 1.038 | 4 | 1.012 | Trace sugar.... | No report. |
| M. | T. L. S.... | 52 | 11 | Arteriosclerosis ..... | 1.040 | 3 | 1.014 | No sugar..... | No sugar. |
| M. | L. S..... | 49 | 18 | Albuminuria ..... | 1.042 | 7 | 1.015 | No sugar..... | No sugar. |
| M. | A. S..... | 56 | 15 | Eye sight failing..... | 1.039 | 2 | 1.016 | Trace sugar.... | 1% sugar. |
| M. | L. S..... | 23 | 13 | Pulmonary tuberculosis.. | 1.047 | 2 | 1.020 | Died while under treatment | |
| F. | B. S..... | 64 | 25 | Arteriosclerosis ..... | 1.036 | 5 | 1.012 | No sugar..... | No sugar. |
| M. | H. U..... | 62 | 17 | Arteriosclerosis ..... | 1.032 | 7 | 1.011 | No sugar..... | Died, 3/11. |
| M. | J. A. W.... | 40 | 9 | ..... | 1.042 | 5 | 1.014 | No sugar..... | No sugar. |
| F. | T. E. W... | 52 | 11 | ..... | 1.038 | 3 | 1.012 | No sugar..... | No report. |
| F. | A. W..... | 47 | 7 | ..... | 1.040 | 5 | 1.014 | No sugar..... | No sugar. |
| F. | J. W..... | 38 | 5 | ..... | 1.042 | 3 | 1.014 | No sugar..... | No sugar. |
| M. | C. W..... | 59 | 13 | Arteriosclerosis ..... | 1.034 | 6 | 1.012 | No sugar..... | No report. |
| M. | A. Z..... | 45 | 7 | ..... | 1.042 | 4 | 1.016 | No sugar..... | 0.5% sugar. |

SUMMARY

| | | |
|---|---|---|
| Number cases | | 83 |
| Number patients died | | 7 |
| Cause of death | Diabetic coma | 3 |
| | Septicemia | 1 |
| | Gangrene | 1 |
| | Pneumonia | 2 |
| Number glucose-free | | 40 |
| Number temporarily glucose-free | | 16 |
| No report received from | | 19 |
| Number died under treatment | | 1 |

### QUANTITY OF FOOD IMPORTANT

One other essential must be made plain to the diabetic and that is the quantity of food eaten is just as important as the kind of food. Too often the patient suffering with diabetes is told to purchase gluten flour or gluten breads (most of which are frauds), and no limitation is put on the amount of these products that may be eaten. It is a fact that many mild cases of diabetes will show a diminution of sugar in the urine almost to the vanishing point when the patient is merely compelled to eat a very moderate ordinary diet. That is to say an antidiabetic diet is not always necessary to reduce the glycosuria; a reduction in the amount of ordinary food will sometimes accomplish the same end. So much for general directions.

### WEIGHING FOOD NOT NECESSARY

It may be said in passing that the attempt to have the patient weigh his food does not give the satisfactory results that might be thought. It is more important to educate the diabetic to control his appetite by sheer force of will than it is to induce him to depend on the scale for his food allowance. Few patients will continue to use a scale after they have left the physician's care, while if they have been taught to exercise judgment and self-control in determining the amount of food they may take, a habit will have been formed that will be their salvation.

For drinking, copious draughts of some mildly alkaline water are desirable. The water should have sufficient salts in solution to increase slightly its natural diuretic effect. Distilled water should not be used, at least for any length of time.

The diet should, at first, be restricted as nearly as possible to proteids and fats, unless the patient shows signs of acidosis or impending coma, in which cases carbohydrates must be cautiously given. It is very essential that the food of the diabetic be well cooked,

so as to tax to the smallest degree the weak digestive system. As the glucose diminishes, fresh vegetables may be added to the dietary, but of such quantity and kind as not to exceed 4 per cent. carbohydrate. Again it should be stated that the quantity of all food—even if it is carbohydrate-free—must be greatly restricted. The number of calories that the body ordinarily requires is no safe criterion of the amount of food that should be given a diabetic. It is not the quantity of food that should be metabolized, but the amount that can be metabolized, that should determine the amount given to the patient. All in excess of the quantity that the patient can actually use burdens the already overtaxed excretory organs and retards improvement.

### OIL IN CONSTIPATION

Olive oil and castor oil, both for the food value and the laxative effect, should be given in all cases in which there is constipation—which means practically all cases. A palatable and efficient emulsion can be made by taking equal parts of olive oil, castor oil and glycerin and emulsifying it with 4 per cent. of Squibb's or Merck's gum arabic.

| | |
|---|---|
| Castor oil ..... | |
| Olive oil ..... | |
| Glycerin āā ..... | 320.0 |
| Gum arabic ..... | 36.0 |
| Flavoring oil (gaultheria or cassia) .... | 1.0 |

The patient must have at least one daily bowel movement and should avoid the ordinary purgatives such as aloes, cascara, calomel, etc.

The diabetic should be kept mentally indolent and physically active; at the end of each day he should be tired, but not to the point of fatigue. As much time as possible should be spent in the open air, and the sleeping-room should be as well ventilated as that of a patient suffering from incipient tuberculosis.

### GLUTEN FOODS

The question of carbohydrate food is, of course, the paramount problem in the treatment of diabetes. The prescribing of so-called gluten flours has, in the past, been one of the most pernicious errors met by the physician who treats diabetics. In the first place, a very large proportion of the gluten flours on the American market are practically worthless as an antidiabetic food; in the second place, physicians in prescribing these gluten flours are likely to give their diabetic patients the impression that a gluten bread is a safe bread.

Many diabetics are killed yearly in the United States from the excessive ingestion of starches taken in the form of gluten breads. Ordinary wheat flour contains from 70 to 75 per cent. carbohydrates, and most of the widely advertised American brands of gluten flour contain all the way from 43 to 73 per cent. carbohydrate. These flours are not only absolutely worthless for the diabetic, but are exceedingly dangerous, because of the false sense of security which the term "gluten bread" carries with it. A flour containing 40 per cent. of starch may be useful in cases of transient glucosuria, but it has absolutely no place in the treatment of true diabetes. It is but fair to say that there are a few diabetic flours on the American market whose starch content brings them within the limit of safety—provided the quantity eaten is most carefully gauged.

Forced some years ago, by the inability to find a safe flour on the market, to devise a starch-poor bread or biscuit I have long given my patients a bread made after the following formula:

| | |
|---|---|
| Unground poppy-seed | 3 lbs. |
| Ground nuts (almonds, pecans, English walnuts or filberts; or a combination of these) | 8 lbs. |
| Eggs | 12 |
| Flour of dried spinach | 1 lb. |
| Salt | to flavor |
| Milk | enough to make a stiff batter |

This batter, shaped into small biscuits or crackers, is baked and, if needed to be kept for any length of time after baking, is thoroughly dried at a mild heat until the moisture is reduced to 0.25 of 1 per cent. The dried biscuits are kept in hermetically sealed tin cans. Put up in this manner they may be kept indefinitely in perfect condition. These biscuits contain about 5 per cent. of carbohydrate.

The drying of these crackers is desirable because it necessitates the most thorough mastication, and thorough insalivation of food is one of the prime requisites of the successful treatment of diabetes. It is for the purpose of favoring mastication that the poppy-seeds are incorporated, although the oil they contain also increases the caloric value of the biscuit. But thorough chewing of the biscuits brings out the flavor of the poppy-seeds, and the pleasure of eating is much increased. The belief, common among laymen, that poppy-seeds contain opium, is, of course, erroneous. Of course these biscuits, like all other starch-poor products, are not so palatable as ordinary bread or biscuits. But they make a very safe and acceptable substitute for bread, and that is all that can be asked for.

### SEVERE CASES

To go back to the patient: If, after two weeks of strict antidiabetic treatment the sugar does not disappear, the patient should be put to bed and placed on a diet consisting of one raw egg and 2 ounces of olive oil, three times or even four times a day, still continuing the free use of mildly alkaline drinking waters. Should the urine show the presence of diacetic acid, the oil must be reduced in quantity and small amounts of carbohydrates given—the patient, meantime, being kept in bed. Sometimes, in cases in which the system is threatened with an overwhelming acidosis, the temporary administration of small quantities of sodium bicarbonate may be tried, although I have seldom seen any good effect from it. This should be given as nearly as possi-

ble midway between meals, so as to cause the smallest degree of interference with digestion. As, however, it will cause some digestive disturbance no matter how carefully administered, its administration should not continue for any length of time.

After getting the patient to the point where the urine is sugar-free, small quantities of carbohydrates should be cautiously added to the dietary. Just as the presence of sugar in the blood establishes a vicious circle and causes the system to become still less able to "burn up" the sugar, so the absence of sugar gives the organism a greater tolerance for this necessary food. The carbohydrate should be added gradually, first at one meal only each day, and that meal preferably breakfast, as metabolism seems more active at that time. As systemic tolerance is increased, the starchy foods may be added to other meals until the point is reached where sugar appears in the urine; when this occurs, all starches should be withdrawn for a day or two and then gradually given again to a point just below that which has been shown to be dangerous.

It is better to add the starch in but one form, rather than several, as the system seems better able to adjust itself to one form of carbohydrate than to several, even though the sum total of starch be the same. What form that should be, can only be determined by experiment. Patients seem to differ in their ability to digest various forms of starch. One man may be more tolerant of bread-starch than of potato-starch; another may be unable to assimilate either bread- or potato-starch and may tolerate small quantities of oat-starch. These individual peculiarities must be ascertained and the results heeded. Another thing to be borne in mind is that all foods that are difficult for the patient to digest—whether they are starch-free or not—should be carefully avoided.

### CONTROL OF THE PATIENT

Every physician who has treated many diabetic patients knows that, on the subject of eating, the dia-

betic is mentally unbalanced. This is true, not only regarding carbohydrate-containing foodstuffs, but regarding the quantity of all foods. Most diabetics suffer from an insatiable hunger. Successful treatment, therefore, depends wholly on the degree of control which the physician can exercise over his patient. In many cases the patients need to be watched with as much care as though they were morphin habitués undergoing antinarcotic treatment.

It is impossible to overemphasize the fact that the quantity of food is as important as the kind of food. It must be evident that a sick person cannot digest the same amount of food that a well person can, and it is the height of folly to permit the diabetic to eat voraciously, even of foods that are absolutely starch-free.

In the case of children it is practically always essential to put the patient in the charge of a competent disinterested person, such as a nurse. Experience has shown that relatives, especially parents, are utterly unable to withstand the tears and pleadings of the child for the deadly carbohydrates which its system craves and for which its whole being cries out. It is seemingly impossible to bring the layman to a full realization of the fact that the sugars and starches, which in health are harmless and necessary and which form so important a part of his daily dietary, are to the diabetic the most deadly and overwhelming poison. In spite of the usual doleful prognosis given in cases of juvenile diabetes, in cases in which the child can be absolutely controlled, the outlook is by no means so black as it is usually painted. This careful supervision must extend over years of time, as the child's system has to be "rebuilt."

Nor are children the only ones who need careful watching and oversight. One of the essentials to successful treatment is that the physician shall see the patient daily until the disease is well under control. A specimen of urine should be brought each day and an increase in the daily output of sugar calls for a careful

inquiry into the dietetic and hygienic incidents of the day before. It should be insisted that the patient write down and bring a list of the kind and amount of food eaten each day. This not only permits of special directions being given regarding certain articles of diet, but it acts as a check on the patient. Many who would not hesitate to vary from the truth when giving a verbal account of the day's dietary will think twice before putting an untruth in writing. Printed diet lists containing general instructions should be given to every patient, while specific written directions should be given to every individual according to his needs.

Diabetes has already been compared to chronic morphinism or alcoholism, and so far as the principles of treatment are concerned the simile is a good one. The personality of the physician is of great importance. The patient must be impressed with the need of obeying instructions. We are creatures of habit and in the diabetic there is usually a vicious dietetic habit to overcome. Without the hearty cooperation of the patient the successful treatment of diabetes is impossible.

### A TYPICAL CASE HISTORY

The following case history may be given as fairly typical of the patients that make up the majority of those treated:

*Patient.*—Swede, aged 40, married, father of five children, a carpenter by trade, consulted Dr. A. J. Ochsner because his hands and feet were cracked and bleeding. Dr. Ochsner after diagnosing the condition as one of diabetes, did not treat the patient but referred him to me for treatment.

*History.*—He had the disease, to his knowledge, for about 18 months when first seen. He had taken codein and arsenauro in large doses and over a long period; had been permitted to eat all the so-called gluten bread that he wished, and no restriction had been placed on the amount of starch-free foods that he had taken. He had been given a diet slip issued by a proprietary house and permission had been granted to eat any of the foods that the list did not prohibit. Before the diabetic condition developed he had eaten large quantities of partly cooked starches, had bolted his food and had partaken of a

badly balanced diet; one containing large amounts of carbohydrate.

*Condition When Examined.*—The patient was passing from 4 to 5 liters of urine daily of a specific gravity of 1.046. There was no albumin and but occasional casts. The skin on the hands and feet was dried, cracked and bleeding.

*Treatment.*—Twelve glasses (8-ounce capacity) daily of mildly alkaline water was immediately prescribed. All so-called gluten foods were immediately withdrawn and the starch-poor (5 per cent.) biscuits previously described were substituted. The amount of all food—starch-free and otherwise—was greatly reduced. Castor oil in doses sufficient to overcome the constipation was given, but no other drugs were used. The glycosuria gradually diminished and finally after four weeks entirely disappeared.

*Subsequent History.*—No return of the glycosuria had occurred up to the time of his death from pneumonia eleven years later, during which period he returned for examination five times at intervals of about two years. During this entire time the patient tested his own urine with urinometer regularly according to instructions that are given during treatment to all adult patients.

## SUMMARY

In brief, then, the following points are essential to the successful treatment of diabetes mellitus:

1. To impress on the patient that after his apparent recovery continued care in eating is essential to continued health.

2. To dispense, as a general thing, with such drugs as codein and arsenic and to make the patient rely practically entirely on the diet and hygiene.

3. To insist on the restriction of the quantity of food just as much as of the kind.

4. To overcome constipation by the use of castor oil and olive oil or by the use of a mixture of these two with glycerin.

5. To insist that the food must be thoroughly masticated.

6. To restrict carbohydrates at the outset to the smallest possible amount consistent with safety.

7. To add starches gradually in but one form rather than in several until the point of tolerance has been reached.

8. To eliminate from the dietary those articles of food that have been found to be difficult of digestion, even in health, though their starch-content may not be objectionable for a diabetic.

9. One of the most important aids, the patient to have copious draughts of some mildly alkaline water.

10. Above all, to impress the patient with the fact that his disease is essentially the result of vicious dietetic habits and that it is useless for him to expect any favorable results so long as the habit is persisted in.

BIBLIOGRAPHY

Sutton, H. H.: Diabetes Mellitus, Med. Stand., December, 1905.

Love, C. A.: Dietetic Treatment of Diabetes Mellitus, Western Med. Rev., December, 1905.

Williamson, R. T.: Dietetic Treatment of Diabetes Mellitus, Practitioner, April, 1906.

Livengood, H. R.: Diabetes Mellitus in Children, Med. Rec., April 28, 1906.

Tyson, J.: Management of Cases of Diabetes Mellitus, Therap. Gaz., Dec. 15, 1905.

Croftan, A. C.: Practical Points in the Dietetic Treatment of Diabetes Mellitus, Therap. Gaz., April 15, 1906.

Rothwell, P. D.: Diabetes Mellitus, Denver Med. Times, 1906.

Crews, G. B.: Case of Diabetes Mellitus, Denver Med. Times, October, 1906.

Lenne: Dietetic Treatment of Diabetes, Berl. klin. Woch., xliii, 19.

Einhorn, Max: Dietetic Treatment of Diabetes, THE JOURNAL A. M. A., Dec. 29, 1906.

Wilson, W.: Diabetes Mellitus—Etiology and Therapeutic Possibilities, Texas State Jour. Med., June, 1906.

Tyson, J.: Management of Cases of Diabetes Mellitus, Med. Exam. and Pract., May, 1906.

Hart, T. S.: Rational Treatment of Diabetes Mellitus, N. Y. Med. Jour., Sept. 15, 1906.

Greedy, F. A.: Treatment of Diabetes Mellitus, Denver Med. Times, October, 1906.

Charles, J. R.: Treatment of Diabetes with Secretin, Bristol Medico-Chir., September, 1906.

Monroe, T. K.: Diabetes, Press and Circular, March 20, 1907.

Seabrook, C. C.: Diabetes Mellitus and Its Curability, Jour. Kan. Med. Soc., December, 1906.

Treatment of Diabetes with Extracts of the Mucosa of the Duodenum, Editorial in THE JOURNAL A. M. A., Feb. 23, 1907.

Winton, A. L.: Diabetic Foods, THE JOURNAL A. M. A., June 29, 1907.

Tyson, J.: Treatment of Diabetes Mellitus, THE JOURNAL A. M. A., Nov. 9, 1907.

Osborne, O. T.: Diabetes Mellitus, Am. Jour. Med. Sci., April, 1908.

Freund, H. A.: Treatment of Diabetes Mellitus, Jour. Mich. State Med. Soc., February, 1908.

Baer, J.: Diabetic Acidosis and Treatment of Diabetic Coma, Therap Monats, June, 1908.

Schmidt, A.: Importance of Cellulose in Diet of Diabetics, Deutsch. Med. Woch., Nov. 19, 1908.

Janeway, T. C.: Dietetic Treatment of Diabetes, Am. Jour. Med. Sci., March, 1909.

Croftan, A. C.: Oatmeal in Diabetes, THE JOURNAL A. M. A., April 24, 1909.

Rudisch, J.: Atropin in Diabetes, Med. Rec., June 26, 1909.

Hall, A. J.: Effects of Certain Drugs in Diabetes, Quarterly Jour. of Med., July, 1909.

Rudisch, J.: Treatment of Diabetes, THE JOURNAL A. M. A., Oct. 23, 1909.

Magnus-Levy, A.: Antidiabetic Foods on Market, Berl. klin. Woch., Feb. 7, 1910.

Lintz, Wm.: Practical Deductions from Urinary Findings in Diabetes, THE JOURNAL A. M. A., March 1, 1910.

Diabetes: Editorial THE JOURNAL A. M. A., Dec. 17, 1910.

Wallace, G. B.: Recent Advances in the Treatment of Diabetes, THE JOURNAL A. M. A., Dec. 17, 1910.

Newcomb, C. F.: Diabetes Mellitus, Illinois Med. Jour., December, 1910.

Lemann, I. I.: Diabetes Mellitus Among Negroes, New Orleans Med. and Surg. Jour., January, 1911.

v. Noorden, C.: Diabetes Mellitus, Med. Klin., Jan. 1, 1911.

Gilbride, J. J.: Functions of Stomach in Diabetes Mellitus, THE JOURNAL A. M. A., Feb. 18, 1911.

Forchheimer, F.: Medicinal Treatment of Diabetes Mellitus, Am. Jour. Med. Sci., February, 1911.

Foster, N. B.: Dietetic Treatment of Diabetes Mellitus, Am. Jour. Med. Sci., February, 1911.

Lichtsitz, L.: Treatment of Diabetic Acidosis, Therap. Monatsh., February, 1911.

Magnus-Levy, A.: Diabetic Acidosis, Bull. Johns Hopkins Hosp., February, 1911.

Kolisch, R.: Carbohydrate Courses in Diabetes, Med. Klin., March 5, 1911.

Carter, H. S.: Treatment of Diabetes Mellitus, with Table of Carbohydrate Equivalents, Med. Rec., April 22, 1911.

Labbe, M., and Violle, L.: Acidosis and Diabetic Coma, Presse méd., April 8, 1911.

## ABSTRACT OF DISCUSSION

DR. ROBERT T. MORRIS, New York: I wish Dr. Hodgson had described post-mortem examination of the pancreas in his report on cases of diabetes. An interstitial pancreatitis, toxic in origin, squeezes out the islands of Langerhans in a proportion of cases of diabetes, and this fundamental cause for some cases of diabetes has been mostly overlooked. Go back of every case of diabetes. Speak of the fundamental causes. Refer to diabetes as a symptom only. You may have to go back to a fibroid appendix, a loose kidney, eye-strain, cholecystitis and the whole chain of factors in the production of toxic influence from the bowel. This toxic influence often induces an interstitial pancreatitis, the islands of Langerhans

are squeezed out and diabetes results as a terminal symptom. Anything which irritates the floor of the fourth ventricle of the brain may have diabetes as a terminal symptom. It is not enough to speak of errors of digestion when discussing the subject of diabetes. Go back a step farther and tell us what is causing the errors of digestion. Surgeons have to deal with diabetes only when the hygroscopic sugar in the blood abstracts water from all body cells, and causes surgical conditions, or interferes with repair in surgical conditions of other origin; but we know that physicians as a rule are not going far enough back in their treatment of diabetics. We know they are not going back to the primary causes for the indigestion which leads to the toxemia which injures the pancreas and ends in the symptom known as diabetes. Examine the pancreas post mortem in more cases, and give us reports on unsuspected interstitial pancreatitis.

DR. EDWARD F. WELLS, Chicago: No foundation for the treatment of diabetes can be considered complete until there has been added to the nosologic diagnosis another and broader one, which may with propriety be termed a therapeutic diagnosis. My practice is as follows: The patient, whom we will assume to be somewhat beyond middle age, continues the diet to which he is accustomed for three days, during which time daily examinations are made of the twenty-four hours' urine. He is now placed on a diet from which carbohydrates are closely excluded, and this is continued until daily analyses show absence of urinary sugar, or until it declines to a point below which it will not descend. There is now added to the diet, carbohydrates, as for example, bread, in definite amounts, which are daily increased until sugar reappears, or increases, in the urine. A daily carbohydrate dietary contingent which falls well short of the patient's glycogenic capacity, as above determined, should be his limit in this class of foods. It is interesting to note that in these cases an increasing tolerance is developed by keeping the sugar out of the urine, or by keeping it down to the lowest possible level. Therefore, about twice a year the test is repeated, in order that, should such increased tolerance develop it may be discovered and measured, with a corresponding readjustment of the carbohydrate content of the dietary. Not only does this method permit intelligent management, but it necessitates taking the patient into partnership in the study and management of his case, thereby maintaining his interest through the many years during which the treatment must continue, which is until death ensues. These patients never recover; but if they receive such proper management as may be readily given them, they need not die from, although they will die with, diabetes.

DR. HENRY B. FAVILL, Chicago: I am very much impressed by what Dr. Hodgson says as to his accomplishments in cases of diabetes taken at random, but my own success has been

various and not altogether satisfactory. I have no hesitation in subscribing to the detail which he sets forth, but I have not the least expectation of securing in general the percentage of satisfactory results which he can show.

Classification of glycosuria is difficult and at present not authoritative. It is to some extent a matter of words. What is the dividing line between "glycosuria" and "diabetes"? Is there a scientific distinction? Is it a matter of degree or is it a matter of personal equation and judgment? Is it not somewhat a matter of temperament on the part of the physician who classifies? Although I am in substantial accord with what Drs. Morris and Wells have stated, I still am at sea at this classification. In the course of the year I see many cases showing sugar in the urine. I have not called them diabetes, however, unless the sugar has persisted. A case of glycosuria which clears up temporarily and remains clear for a reasonable length of time I do not call diabetes. However, what right have I to say that one is a case of diabetes and the other is not? This brings us really down to the practical question.

The broad handling of glycosuria, in my opinion, is based on a few facts. 1. There is a transitory glycosuria which is very transitory and unquestionably dietetic. 2. There is a glycosuria much more grave and largely amenable to dietetic regulation. 3. There is a glycosuria which is undoubtedly pathologic in its anatomy, which is only slightly amenable to regulation of the diet. This last is fundamentally progressive and the cases are more or less hopeless. I think we can say that we have all sorts of gradations in these questions and the question is not one particularly of a pathologic classification but a matter of judgment—that is to say, the interpretation of the practitioner.

The principles of dietetics have been thoroughly well stated, particularly with regard to limitations in amount and as to bringing the total food down to what the individual can safely handle. There is a matter which has not been mentioned which I think is of importance: the reciprocal balance between the capacities for assimilating carbohydrates and proteins. In a large percentage of patients, particularly those of a full habit, the capacity for handling carbohydrates can be pushed to a higher point by reducing the protein demand on the system. So far as my own observations have gone, individuals with glycosuria or with diabetes, who are well nourished, quite plethoric, respond quickly and favorably to the diminishing of their nitrogenous intake. The benefits from this process as a rule are greater than that from cutting down starches. I wish to emphasize also what Dr. Hodgson has said about cutting down the total food to the point of tolerance without any regard at first to theoretical caloric value.

Dr. R. Wernigk, Los Angeles, Cal.: There is one thing I believe to be of importance, that has not been mentioned, pertaining to the administration of alkali by the stomach. In

children, I prefer to administer the alkali by way of the bowel. The acid gastric juice stimulates both the liver and pancreas to action; and the administering of large doses of alkali by way of the stomach naturally interferes with the acidity of the stomach contents. I find that by administering alkali by the bowel I get far better results. Of course, in acute cases in which we do not want to stimulate the pancreas, we must administer alkalies by the stomach. Even after the abatement of the condition, it is advisable to give the alkalies by the bowel. Fifteen or twenty years ago, I had a horror when called on to treat a case of diabetes occurring in a child. I am glad to say, however, that in later years I have experienced a change of opinion, and I have been able to save several children. I have among my patients young girls and boys who were suffering five or ten years ago from diabetes. After acute diseases, frequently as a result of infection or inflammation, the islands of Langerhans are involved, and the functions of the pancreas interfered with, and as we often see the hydrochloric acid reappear in an acid stomach after prolonged absence, so also does the pancreas frequently resume its functions after prolonged treatment, unless, of course, the islands of Langerhans are totally destroyed.

DR. A. J. OCHSNER, Chicago: Naturally surgeons get many cases of diabetes; they come to us, or are sent, because of the accompanying gangrene. Twenty years ago we expected after an amputation of a limb because of diabetic gangrene, to have in a large proportion of cases, diabetic coma and death within forty-eight or seventy-two hours. Since that time my opinion has changed. Because of what I have learned from Dr. Hodgson I find that in my diabetic amputation cases the wounds heal by first intention. Dr. Hodgson has had these patients heal by first intention. After Dr. Hodgson has had these patients under observation for three or four weeks one cannot get them to eat anything he has forbidden. He impresses certain ideas on his patients and the patients stand by them. Some of Dr. Hodgson's patients under my observation have followed out his ideas and his directions for as long as sixteen years and have been free of sugar for this entire period of time. He got these patients to believe that they should not eat four times as much as was necessary to be well; he got them to practice what he taught, and this, I believe, is the secret of his success in handling cases of diabetes.

I have operated on a large number of patients with pancreatitis and I have found a few suffering with diabetes; but this proportion was exceedingly small. Unfortunately, I am not in a position to make autopsies in cases of death of patients with diabetes. The same as most of you, I must go by what I find in the literature concerning the results of pancreatitis, and especially the effects of pancreatitis on the islands of Langerhans. That there is danger from pressure on the

islands of Langerhans is undoubtedly true. If the patient does not die, how can we say that there is pressure on the islands of Langerhans as the result of diabetes? If we had a large number of cases coming to us for operation with pancreatitis, suffering also from diabetes, and if we could make autopsies in these cases, this point could be proved. But this is a point that is well worth bearing in mind and following out; in every case of diabetes resulting in death there should be a necropsy. Another thing of importance is to get people to understand that they are not well because of taking this, that or the other medicine; they get the idea that it is this or that medicine that cures them when, in fact, it is the dietetic treatment that results in good.

DR. A. J. HODGSON, Waukesha, Wis.: Details are necessary, of course, but to give the details of 100 patients suffering from diabetes, especially with regard to the qualitative and quantitative values of the food, would be almost impossible. Such details would fill many books. It should be remembered that every patient must be treated individually. No set rules will apply to all. With regard to the cases of pancreatitis, I am not certain as to the causes of this manifestation of diabetes. I have met with cases of pancreatitis, but I have never yet met with anyone who could inform me as to the causes. When these patients died and were brought to post mortem, the condition was found but it was not diagnosed during life. I think, however, that the long-continued influence of the toxemia, the toxemic poison, is a sufficient cause of the degeneration found, and thus a cause of the pancreatitis. I wish to emphasize the fact that no one can have sugar in the urine for any length of time without having some pathologic changes in the body. One of the symptoms which should be looked for is the loss, or partial loss, of sight; this is not due to cataract but possibly to an anemic condition of the retina caused by the presence of sugar in the blood. Many of these conditions have been mentioned in my paper. I have never seen any benefit result from the giving of strong alkalies that has not been secured by giving large draughts of a mildly alkaline water. I do not believe that the administration of sodium bicarbonate has any value in the curing of this trouble. Give plenty of mildly alkaline water; this is far better, in my opinion, than giving the strong alkalies.

# BUBONIC PLAGUE

## WITH SPECIAL REFERENCE TO THAT OF GROUND SQUIRREL ORIGIN *

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Bubonic plague is a subject with which, fortunately, few of us have to deal. The practitioner in California, however, especially if his lot has been cast in the rural communities, must always keep the disease in mind when any acute febrile case comes under his observation. It is my intention to discuss only the isolated cases that occur in the country districts. Those that have been seen in San Francisco and in Oakland at various times between 1900 and 1908 were clearly associated with the presence of plague among rats, while the cases to which I particularly refer are associated with, and due to, the prevalence of the disease among ground squirrels (*Citellus beecheyi*). While plague in man when contracted from these animals is probably not essentially different from that derived from other sources, usually from rats, the cases that have come under observation are sufficient in number to justify us in examining them with care, especially as they are due to infection from a source that is unusual in other countries.

Two or three years after plague had been recognized in San Francisco, several cases of the disease occurred among persons living in the rural districts in the country across the bay from San Francisco. Surgeon Rupert Blue, of the Public Health and Marine-Hospital Service,

* From the Federal Laboratory, San Francisco.

noted in one or two instances that the disease occurred in those who had hunted ground squirrels a few days prior to the onset of the illness, and he suggested that since there had been no contact with human plague, and no known opportunity for infection from rats, the disease might be present in the squirrels, and be communicated from them to man.

During the past three years I have conducted the bacteriologic investigations in eleven cases of plague of ground squirrel origin. Seven of these patients I have seen clinically, and verified the diagnosis by laboratory methods, while in four the diagnosis was made from the bacteriologic examination of tissues taken at autopsy and sent to the laboratory. Six of these patients, all from the known infected zone, gave a clear history of handling ground squirrels within a week prior to the onset of the symptoms. Five gave no such history although they had been in vicinities where plague was known to exist among the ground squirrels at the time, or where it was demonstrated as a result of the investigations set in motion by the discovery of the disease in man. Of these eleven patients, seven were young men between the ages of 13 and 37; one was a boy aged 5; another, a boy aged 7; while two were young women. Six of these proved fatal, while five recovered.

Clinically there were three groups: The severe acute, the mild acute, and the subacute or pyemic. Six belonged to the first group. A typical history of one of these is as follows:

> About a week before becoming ill, the man had been squirrel shooting. The first complaint was of pain in the back and in the groin. There was great prostration. The temperature was 101.4 F., pulse 100. The second day, a swelling was made out in the femoral region. The third day, the patient was delirious and remained so until he died. The highest temperature recorded in this case was 103.8 F. but it usually goes to 105 F. or over. Death occurred on the fifth day of the illness.

One of these cases was rather unusual in that recovery occurred after invasion of the blood-stream by the plague bacillus. The evidence of septicemia was the recovery

of the bacillus from the blood, and the development of secondary buboes in the regions of the various peripheral lymph glands.

The mild cases were four in number; all ending in recovery, but none was so mild as to justify calling it pestis minor. The history of the most recent case is as follows:

There was no evidence of contact with squirrels, but the patient, a girl, lived in a territory that was known to be heavily infected. The first symptoms were headache and fever. These were followed by pain and tenderness in the right groin. The disturbance was so mild that it was thought sufficient to consult a physician by telephone. However, when improvement did not occur, the patient was visited by the medical attendant, who found a temperature of 104 F. There was a bubo in the femoral region. One week after the onset of the illness the glands were removed under an anesthetic. The patient made an uneventful recovery, never having been regarded as dangerously ill.

The subacute class is represented by only one among the squirrel cases that have come under my observation. This has been reported in detail by former Acting Assistant Surgeon W. B. Wherry and myself.[1] These cases of subacute or pyemic plague are seen occasionally in epidemics of rat origin.

The patient was a youth, aged 13, who had been squirrel shooting about five days prior to the onset of the symptoms. The illness began with headache and vomiting. The next day the temperature was 104 F. Forty-eight hours after the onset of the symptoms, the glands in one axilla were found to be much enlarged and very painful. The nature of the disease was not suspected and the glands were excised. On the fifth day all of the superficial glands became swollen and tender. The sputum was blood-tinged, and the patient was evidently quite ill. On the tenth day a pustular eruption appeared and plague bacilli were found in one of the skin lesions. The patient became septic and died on the sixteenth day of the illness. At the post-mortem, caseo-purulent foci were found in the lungs, liver and kidneys, as well as in the lymph glands.

1. Wherry, W. B., and McCoy, G. W.: Jour. Infect. Dis., November, 1909, vi, 5, p. 670.

No case of primary pneumonic or primary septicemic plague attributable to ground squirrel infection has come under observation.

On account of the importance of a diagnosis that cannot be impeached, it is required that all of these cases be verified bacteriologically; a few words may be said, however, about the clinical diagnosis. The onset is usually with fever, headache and pain in the back. Nose bleed often occurs. Several of the cases gave a history of an initial chill. The temperature is usually about 102 F., or 103 F. when the patient is first seen by a physician. A glandular swelling appears, sometimes coincident with the onset of the other symptoms, but usually a day or two later. In eight of the eleven cases, the primary bubo was in the axilla; in three it was in the groin. The gland involved is tender. The outline is lost in an edema that surrounds the parts. Fever and other general symptoms continue from five to eight days, or even longer. In the only cases in which recovery has taken place and the glands had not been excised, suppuration occurred. In the fatal cases, the patient usually dies while the glands are caseous and hemorrhagic and before pus has formed.

It is a pleasure to be able to state that although the disease is rare our recent cases have been recognized as suspicious by attending physicians and by the surgeons who removed the glands.

The bacteriologic diagnosis is made by the examination of a piece of the gland removed at operation, of fluid aspirated from a gland, or of tissue removed at the necropsy. When the smears show a considerable number of pest-like bacilli, a provisional diagnosis is made. The bacillus is isolated by cultural methods and laboratory animals are inoculated. It is the rule that the media inoculated from the bubo show an enormous number of colonies of *Bacillus pestis,* but in one case only six colonies appeared on the three tubes used, showing apparently that bacilli were very scarce. The growth was highly virulent, though the case was a mild one.

An experiment was undertaken for the purpose of ascertaining whether there was any difference in virulence for laboratory animals of the cultures isolated from the mild and from the severe cases of plague in man. Without entering into the details of the experiment I may state that the bacilli derived from mild cases were quite as pathogenic as those obtained from the severe and fatal cases. In other words, the severity of clinical manifestations is due to the varying resistance of the individuals rather than to a difference in the virulence of the organisms causing the disease.

Whenever practicable, the cases are treated with antipest serum, but the majority have come under observation too late to be benefited by it. The other treatment is purely symptomatic.

So much for the subject as regards human plague. I shall now discuss briefly the more important problem, the infection among the ground squirrels. The first proof of plague among the squirrels was obtained in the summer of 1908. Since that time, by an extensive investigation of these animals throughout the state, it has been found that the disease is probably confined to ten counties lying east and south of San Francisco Bay. This work has been carried on by the Public Health and Marine-Hospital Service, the immediate direction being in the hands of Surgeon Rupert Blue. The squirrels are shot and sent to the laboratory where they are dissected and examined.

In the rodents, the disease causes well-marked and readily recognized lesions which vary greatly. The larger percentage of cases are distinctly subacute or chronic, while a smaller number are of the acute type.

The pest bacillus isolated from infected squirrels is, morphologically, culturally and bacteriologically, in every way identical with that isolated from man and from rats. As to its pathogenicity, I may say that the organism appears to be a trifle less virulent than those from other sources; however, no definite statement is to be made on this point.

A very interesting observation is that many of the squirrels from the zone in which plague has prevailed for several years are relatively immune to laboratory infection with *Bacillus pestis*.

During the routine examination of these rodents, we have encountered a disease, the gross lesions of which bear a very strong resemblance to those of plague.[2] It is readily differentiated by bacteriologic methods.

The subject of the transmission of the disease from one squirrel to another, and from these rodents to man, is a very important one, and I regret that we have no conclusive evidence about the mode of infection. We have been able to show experimentally that plague may be carried from squirrel to squirrel by means of fleas. It may also be transmitted by feeding. What evidence we have, largely dependent on the location of the bubo, leads us to suspect that the disease is conveyed in nature by fleas, and possibly by other ecto-parasites. Briefly, this evidence, the importance of which in rat plague has been demonstrated by British workers in India, is as follows: In natural infections in rodents the bubo is found in the region of the peripheral glands, cervical, axillary, inguinal or pelvic. This agrees with the distribution of buboes in squirrels, rats and guinea pigs that have been infected experimentally by fleas, while in rodents infected by feeding, the buboes are always in the neck or in the mesentery. It will be noted that the neck buboes may be acquired in either way, i e., through fleas or by ingestion.

In one of the cases the patient, a boy, was bitten on the hand by a squirrel, and since the primary bubo occurred in the axilla on the same side, it seems reasonable to suppose that the bite infected the boy. This is rendered probable as many plague squirrels have lung lesions. Most of our cases have occurred during the summer months, which is the season of squirrel hunting.

2. Pub. Health Bull. 43, U. S. Public Health and Marine-Hospital Service, Washington, D. C., 1911.

That the mere handling of an infected animal is not very dangerous is shown by the fact that the employees of the service have handled hundreds of plague squirrels without an accident, merely taking precautions against fleas.

The predominance of axillary buboes in human cases would appear to be accounted for by the fact that in handling infected squirrels which may carry parasites, the hands and arms would be more exposed to the attacks of the insects than other parts of the body. We cannot assert positively that parasites carry the disease to man, but it seems to be the most reasonable explanation.

The question might be asked why so few cases of plague in man have resulted from the extensive infection among the ground squirrels. The answer is not quite clear, but leaving aside such matters as failure to recognize or to report the disease, it may be stated that the evidence offered by the examination of infected squirrels leads to the belief that a comparatively small percentage of them have the bacilli circulating in their blood in any considerable numbers. Of about 250 infected squirrels of which we have complete records, only about one-fourth could have been regarded as septicemic at the time they were shot.

The chief menace of squirrel plague is, as has been recognized from the first by all of those who have occasion to deal with the subject, the danger of the infection of the rats of the cities, which might lead to more or less extensive outbreaks among human beings. The discussion of this problem is not within the scope of the present paper.

I wish to acknowledge here my indebtedness to the various physicians in the state in whose practices the cases occurred and who furnished me with the clinical data.

ABSTRACT OF DISCUSSION

DR. EDWARD F. WELLS, Chicago: The paper of Dr. McCoy is a very important one bearing on bubonic plague with special reference to ground squirrel origin. I should like to ask him

for what purpose the animal was killed and what becomes of the carcass? Also does each species have special fleas of its own?

DR. G. W. MCCOY, San Francisco: The squirrels examined have all been killed or caught by hunters employed by the Public Health and Marine-Hospital Service for the purpose of securing specimens in order that the extent of the zone of plague infection may be determined accurately. As to the matter of fleas, in a general way we may say that each species has a special flea of its own, and, judging from what we have learned by experimental work on the lower animals, fleas from one species are capable of carrying the infection to other species, in addition to carrying it among the members of the species to which the particular flea properly belongs.

# SOME APPARENTLY OBSCURE CONDITIONS OF THE GASTRO-INTESTINAL TRACT AND THE PRACTICAL APPLICATION OF THE RÖNTGEN RAY IN THEIR DIAGNOSIS *

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We are not dealing with the obscure conditions of the gastro-intestinal tract as they arise, but mostly with the common pathologic states, often misinterpreted on account of the unsatisfactory methods of diagnosis at the present day. The subject is so broad that we have decided to restrict our paper to the size, position, and motility of the gastro-intestinal tract. Normal patients, or patients with splanchnoptosis with or without intestinal symptoms, constitute our particular theme. Cases of ulcer and malignancy have been omitted on account of limitations of space.

All the cases under consideration have been studied first with regard to the physical signs and the ordinary tests for gastro-intestinal secretions and contents. The Röntgen ray has been used as an aid and confirmatory agent in diagnosis. Whereas due consideration in every case has been given to the history, subjective and objective signs, and examination of secretions, we have found

* From the Edward N. Gibbs Memorial X-Ray Laboratory and the Marcellus Hartley Foundation in Medicine.

progressively downward and they become confirmed the previous diagnosis, it has also shown the error of the previous diagnosis in an astonishing number of cases. A great difficulty in gastro-enterologic work has been the lack of certainty in the results of clinical tests for size, position, and motility of the hollow viscera. The Röntgen ray solves this problem. Every day we meet patients with moderate or severe grades of constipation, not due to obstructions from tumors. They have usually gone the rounds of numerous physicians or dispensaries, and are relieved only by the continuous use of laxatives or cathartics. Their course is nearly always progressively downward and they become confirmed neurasthenics or slaves to the drug habit. Occasionally, without any scientific accuracy on the physician's part, these patients, if they are fortunate, improve by treatment on general principles.

In previous examinations, chemical tests for motility of the stomach and intestine have been unreliable. Peristalsis of the stomach and intestine sometimes can be seen through an abdominal wall that has been thinned out, usually in advanced emaciation. The entire length of time that food takes to pass from the mouth to the anus can be determined by the ingestion of indigestible and non-absorbable foods or chemicals, such as bismuth salts, which can be recognized in the stools. This does not indicate, however, the length of time consumed in digestion by the different portions of the alimentary tract, and is often inaccurate in determining the time of digestion. Tests for determining residual food in the stomach are tedious and very annoying to the patient, and determine only approximately the final result. This, with our other important data, can be shown by the Röntgen ray, in a properly conducted series of plates.

Radiographs of the alimentary tract after the administration of some insoluble substance which obstructs the Röntgen ray, such as the bismuth salts, have been used

in Europe since 1904, by Rieder,[1] Holzknecht,[2] C. Kaestle and J. Rosenthal,[3] Franz M. Groedel,[4] A. F. Hertz,[5] and others; and in this country by G. E. Pfahler,[6] Hulst,[7] Pancoast,[8] Cole,[9] and others. The methods will soon be universally applied. Rieder was the first to give large amounts of bismuth salts. He gave from 40 to 50 gm. of bismuth subnitrate in a meal of boiled rice, barley broth, potato puree, spinach, or boiled meat. The bismuth can be administered by mouth or by rectum. Haenisch[10] was the first to give the bismuth per rectum, in the following formula: bismuth subcarbonate 75 gm., bolus alba 300 gm., water 1,000 c.c. We use the bismuth rectal injection and find it a valuable adjuvant to the method by mouth. Kaestle used zirconium oxid instead of bismuth because it was more insoluble. Of the salts of bismuth, the subnitrate was at first extensively used, but it has caused toxic symptoms. Cases of poisoning due to the impurities in the preparation, or to the absorption of the nitrites formed in the intestine, have been reported by E. G. Beck,[11] W. Alexander,[12] L. Lewin,[13] and many others. The subcarbonate of bismuth is apparently non-poisonous and acts in the same way as the subnitrate toward the Röntgen ray. We have had no toxic symptoms in over forty tests in which large quantities were given. Examination of the bismuth stool shows the bismuth passed through chemically unchanged.

Milk, as representing a suitable form of food, is now being used as a menstruum for the bismuth. A serious

1. Rieder, H.: München. med. Wchnschr., August, 1904.
2. Holzknecht: Berl. klin. Wchnschr., Jan. 29, 1906; also: Mitt. a. d. Lab. f. radiol. Diag. u. Therap., Vienna, No. 1, 1906.
3. Kaestle, Reider and Rosenthal: Arch. Röntg. Ray, June, 1910.
4. Groedel, F. M.: Arch. Röntg. Ray, September, 1910, p. 156.
5. Hertz, A. F.: Discussion on Groedel's paper, Arch. Röntg. Ray, September, 1910.
6. Pfahler, G. E.: The Journal A. M. A., Dec. 21, 1907, p 2069.
7. Hulst: Physician and Surg., Detroit, 1905, xxvii, 391.
8. Pancoast: Univ. of Penn. Med. Bull., August, 1906.
9. Cole, L. G., and Einhorn: Radiograms of the Digestive Tract, New York Med. Jour., Oct. 8, 1910.
10. Haenisch: Rep. Am. Röntg. Soc., Sept. 29 to Oct. 1, 1910.
11. Beck, E. G.: New York Med. Jour., Jan. 2, 1909, p. 16.
12. Alexander, W.: Deutsch. med. Wchnschr., 1909, xxxv, 877.
13. Lewin, L.: München. med. Wchnschr., 1909, lxi, 643.

objection to ordinary milk is the early precipitation of the bismuth, but this can be overcome by the use of the fermented milks which hold the salts in suspension for a much longer time. Our experiments with bismuth suspended in various media demonstrate that the salts mixed with the fermented milk remain in suspension longer than in other fluid foods, as malted milk, sweet milk, buttermilk, and chicken soup. The next best substance is a thick chicken soup. (Fig. 1.)

For the average adult, 75 gm. of bismuth subcarbonate suspended in 500 c.c. of fermented milk is given with the stomach empty. Previous catharsis is unnecessary and inadvisable. The diet for the previous twelve hours must be light and exclusive of meat, fruits, and vegetables. All medication is omitted.

The radiographs have all been taken with the patient in the standing position. The distance from the anode to the plate is 24 inches, with the plate anteriorly and the anode on a level with the umbilicus. The illumination is dorsoventral, with one or two lateral views, as the occasion demands. The duration of the exposure is from one-sixth to four seconds, mostly under one second. It requires an average of from eight to twelve radiographs to examine a patient. Occasionally, a second series is necessary for a control, or a rectal injection to corroborate the colon findings. For experimental purposes, more plates have been taken than are ordinarily necessary for a routine examination. We find that the radiographs after the rectal injection do not give as natural an appearance to the colon as those taken after the administration of the bismuth by mouth. The plates can be taken much sooner, however, as the bismuth mass reaches the cecum within fifteen minutes and is then rapidly expelled per rectum.

We always try to make a primary, a secondary, and a final diagnosis. The primary diagnosis is made from the history, the physical examination, the examination of the gastric contents after a test-meal, and the exam-

ination of the feces and the urine. Other examinations are made as the occasion arises. The primary diagnosis is made previous to any consideration of the Röntgen ray.

The secondary diagnosis is made wholly from thorough consideration of multiple Röntgenograms, taken seriatim after the bismuth meal. In every case, the exposures are continued until the last trace of bismuth has left the alimentary tract.

The final diagnosis is made by carefully comparing the primary and secondary diagnoses and weighing the preponderance of evidence offered by the symptomatology.

In estimating the position of the viscera, our technic is to place markers on (1) the tip of the ensiform, on (2) the umbilicus, over (3) the tip of the ninth right costal cartilage, and on (4) the anterior superior spine of the right ilium. The umbilicus, contrary to what we expected, appears to be a fairly well-fixed point, except in very pendulous abdominal walls. It must be remembered, however, though these landmarks are sometimes uncertain, yet if their location is abnormal it is evident on physical examination, and hence allowance can be made.

We shall first mention some of the results, quite constant in nearly all our cases. Our studies on the esophagus have been entirely too superficial as yet to warrant the findings being chronicled. The points in fixation of the stomach agree with those described by anatomists. They are the esophagus and distal end of the first portion of the duodenum, which latter point anatomists say is firmly attached by the duodeno-hepatic ligament (Piersol[14]). In a normal, or at least a non-ptosed well-filled stomach, the shadow of the distal end of the first portion of the duodenum reaches the level of the upper border of the second lumbar vertebræ. The outline of the pylorus is situated opposite the junction of the second and third lumbar vertebræ. For the purpose

14. Piersol, George A.: Human Anatomy, 1909 ed.

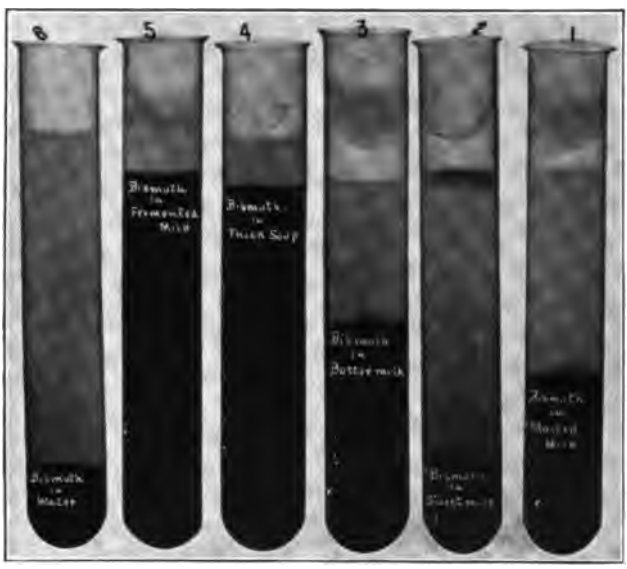


**Fig. 1.—Radiograph of substances used for Röntgen-ray test-meals. Each test-tube contains an equal amount of bismuth subcarbonate. It shows the amount of settling fifty hours after suspension. 1. Malted milk and acacia. 2. Sweet milk. 3. Buttermilk. 4. Chicken soup. 5. Fermented milk. 6. Water and acacia. Note the remarkable stability of the suspension of the bismuth in the fermented milk.**

Fig. 2.—Radiograph taken five hours after the ingestion of a bismuth meal (Case 1). A, base; V, the tip of the vermiform appendix; U, umbilicus; T, transverse colon; H, hepatic flexure; B, remnants of bismuth in coils of small intestine; S. S., anterior superior spines.

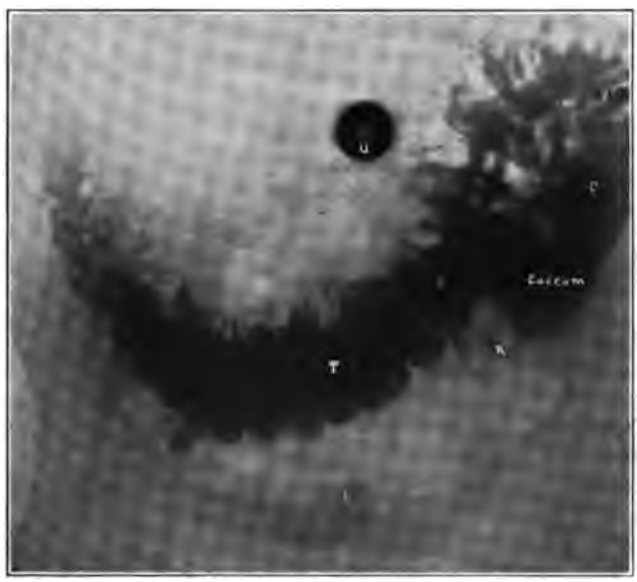


Fig. 3.—Radiograph taken twenty-six hours after the ingestion of a bismuth meal (Case 1). T, transverse colon, now become U-shaped; A, vermiform appendix, bent on itself; F, traces of bismuth in the sigmoid flexure; C, ascending colon. The lighter areas in the upper part of the colon are due to gas formation.

Fig. 4.—Radiograph taken three hours after the ingestion of a bismuth meal. This shows the rapid passage of food through the stomach and small intestine. The colon is dragon-shaped. H, hepatic flexure; T, transverse colon; D, splenic flexure; G, traces of bismuth in the stomach; B, bismuth in the small intestine. Case 6 [not reported in detail].

of classification, we consider that if the lesser curvature is well up above the upper margin of the umbilicus, the stomach is not ptosed. The shape of the stomach varies according to the position of the subject. When the patient is in the standing position, in the greatest number of cases, the shape of the stomach resembles that of a fish-hook, and when in the recumbent ventral position, it simulates a steer's horn. This modifies former anatomic views based on dissections in the dorsal decubitus. When the patient is in the standing position, the long axis is vertical; when he is in the prone position, the long axis in the same subject may be oblique or almost transverse.

In order to determine accurately the size, shape, and position of the stomach, studies of plates made within a few minutes after ingestion of the bismuth meal should be made. During activity of the stomach, peristaltic waves can be seen distinctly as constrictions on the greater and lesser curvatures. These are differentiated from permanent constrictions by the changes in form of the organ in the succeeding plates or by the fluoroscope. The former is, in our estimation, more accurate and practical than the latter. The cardiac end of the stomach empties very quickly and shows the rugæ often plainly marked out by the bismuth. In cases of gastric fermentation, the gas rises in the cardiac end and pushes up the diaphragm, as can be well demonstrated in the radiograph.

The average time required for the normal stomach to empty itself completely of a full bismuth meal is, in our experience, from two and one-half to four hours. It is difficult to prove atony of the gastric musculature, but stasis and permanent pouches can be demonstrated, some of the bismuth remaining in the lower pole as long as ten hours after ingestion.

The motility of the stomach in nearly all cases appears to be most rapid during the early part of digestion. Some stomachs seem to rest after the first thirty minutes

to an hour. After that, they still contain about one-quarter of the amount of the original contents, which is discharged in a variable time. The end motility of the stomach is apparently not influenced by the amount of free hydrochloric acid in the gastric contents. The early activity in certain cases of hyperchlorhydria is increased, however. This is demonstrated by the serial radiographs taken up to the final emptying of the organ. The dilated stomachs almost invariably show a slow motility, especially in completion of the act.

The study of the small intestine has so far been unsatisfactory, especially so of the duodenum, on account of the rapidity with which the bismuth meal passes through this part. The first portion of the duodenum can usually be identified by a small mass of bismuth, the so-called "bishop's cap," separated from the pyloric antrum by the outline of the pyloric muscle. The pyloric ring, as thus seen, averages 3/16 of an inch in width. In most of our cases, splashes of bismuth appeared in the jejunum within a few minutes after the entrance of the meal into the stomach, and it is the exception to find the small intestine free from bismuth within ten minutes after taking the food.

The course of the bismuth in the jejunum is first to the left iliac region, but it quickly settles in the median line. It appears between the umbilicus and the brim of the true pelvis in non-ptosed conditions and enters quickly the true pelvis in ptosed states.

We find the progress of the bismuth in the small intestine to be comparatively rapid. In the twenty-seven cases studied for this paper, the earliest time within which the bismuth has reached the cecum was one hour. This occurred in two adults, and in three children about twelve years of age, one of whom had a pan-visceroptosis. Rieder[1] and Goldthwaite[15] consider two hours to be the most rapid time in which the bismuth can reach the cecum, while Groedel and Hertz say that they have not seen the bismuth reach the cecum in two hours, and that

four hours is the shortest time it takes. In our slowest cases, so far, the bismuth has taken five hours to reach the cecum. The average time seems to be two hours. Complete emptying of the small intestine can be determined in only nine out of the twenty-seven cases. In these cases it averages about six hours, and varies from four to seven hours. The estimation of the time is rendered uncertain by a dilated, sacculated, or "residual" stomach, which constantly sends over splashes of bismuth into the small intestine until the organ has completely emptied itself.

Normally, the cecum is always situated well above the brim of the true pelvis. When the colon is ptosed, the cecum lies near the brim and in severe cases often hangs over into the true pelvic cavity. Dilatation of the colon appeared in eight cases, in which the colon had not been emptied in forty-eight hours.

In three of our cases, the vermiform appendix can be plainly seen, the lumen being patent and filled with bismuth. This occurred in one case after a cecum had become much engorged, and in another before the cecum had been filled. In these three cases, the situation and size could be proved. In one of the patients the bismuth remained in the appendix four days after the cecum had been emptied.

In one of our patients, with a complete transposition of all the viscera and a coloptosis, a subacute appendicitis seemed probable. The radiograph demonstrated the cecum well below the line leading from the anterior superior spine to the umbilicus and on the left side. McBurney's point, where the place of tenderness existed, corresponded to the hepatic flexure. An operation has not been performed, as the pain and tenderness were probably caused by a localized colitis, as evidenced by the mucus in the stools. The bismuth radiogram proved the locality of the cecum, and, if it did not absolutely disprove the diagnosis of appendicitis, at least showed that the patient's appendix was on the left side and

well down in the pelvic cavity. The patient improved under treatment, which was general, and local for the colitis, with an abdominal belt for support for the coloptosis.

Our results as to the position, size, shape, and motility of the colon have been very satisfactory. The organ can be readily identified by its size, position, and sacculations. We have classified the cases into (1) normal colons, (2) abnormally long and looped colons, (3) ptosed colons, with or without abnormal length and loops, and (4) abnormally short colons. As to the shape of the colons, the following terms have suggested themselves to our minds: (a) straight, transverse colons, the strictly normal; (b) the U-shaped colon, caused by one large loop, dipping down toward the pelvis; (c) the V-shaped colon, which is similar; (d) the double U-shaped colon, with one loop from the hepatic and another from the splenic portion of the transverse colon; (e) the W-shaped colon, similar to the last; (f) the diamond-shaped colon, with the transverse portion running abruptly upward from the hepatic to the splenic flexure; and (g) the dragon-shaped colon. Our control radiographs show the constancy in the shape and position of these colons, and in our estimation prove them to be peculiar to the individual. In some cases, hidden folds in the colon occur which give in later radiographs, after the colon is well filled, a much longer and looped appearance.

A ptosis of the colon is recognized by the low position of the caput coli and of the hepatic flexure. The hepatic flexure is normally at or above the level of the umbilicus. The loops of the colon may exist without a coexisting ptosis, as shown in some of our cases. The most constant point of fixation of the colon is at the splenic flexure where the intestine is attached by the phrenocolic ligament to the left abdominal wall under the spleen (Piersol). The average height of the splenic flexure, in our cases, is 4 inches above the umbilicus, a point

which varies but little except in some extreme cases of coloptosis.

Motility of the colon varies, often out of proportion to its length. The motility in ptosed colons we think is always slow.

The sigmoid flexure has, as we expected, a variable length and size. In normal cases it is situated well within the pelvic brim and does not pass much to the right of the median line. The length of abnormally long sigmoids may be estimated by the distance to the right of the median line and the height to which they extend. In three of our cases the shadows of the sigmoid and cecum impinge. In two of the cases long and dilated sigmoids are present, associated with colons of normal length. In one of our patients the sigmoid and rectum held the bismuth for over seventy-five hours and it was forty-eight hours more before the patient passed bismuth in the stool. This made a total residence of the feces in this part of the intestinal tract of over five days. The patient had a long-standing constipation, followed by hemorrhoids, which were excised. The radiographs show a long, looped and ptosed colon, with a long and tortuous sigmoid and upper portion of the rectum.

Our treatment for these cases of gastroptosis, enteroptosis and coloptosis consists of an abdominal wall support, often reinforced by two horsehair pads arranged ventrally, so as to support the colon. Goldthwaite's posture[15] taken immediately after eating, with the patient on his back, hips and thighs elevated, has been tried successfully in a number of cases.

### CASE REPORTS

CASE 1.—M. McD., a woman aged 27, child's nurse, single, ever since childhood had been constipated and had to take cathartics or laxatives. For the past two years she had been getting worse, vomiting having occurred from one-quarter to one-half hour after meals. She had pain, which was most marked in the epigastrium, but which also at times extended

15. Goldthwaite, J. E.: Boston Med. and Surg. Jour., May 19, 1910.

lower down on the right side of the abdomen and into the right hip and leg. Distress and soreness after eating were invariably present over the sternum. During the summer and fall of 1910 she developed hemorrhoids, which became inflamed and were removed in January, 1911.

After the operation, the patient's symptoms continued; the obstinate constipation could not be relieved by medical means, the chief of which were olive oil internally, ordinary enemas, and olive oil per rectum, colon massage, and vibration. Analysis of the gastric contents showed traces of free hydrochloric acid. The stools were very dry, hard and contained undigested food.

In May, 1911, the bismuth-Röntgen-ray test was made. This showed a stomach of normal shape and size, but ptosed, with a complete emptying in three hours. The bismuth reached the cecum in two hours, and the small intestine was completely emptied in five and one-half hours. Four hours after the ingestion of the bismuth, the cecum and part of the transverse colon were filled, the transverse colon straight, and the hepatic flexure 2 inches above the umbilicus, and therefore no ptosis apparent. The shadow of the bismuth in the ascending colon was so heavy that in consideration of the next picture the colon seemed to be folded on itself (Fig. 2.) One hour later the bismuth meal had not made any progress, but the apparent churning motion and the weight of the residue had dragged down what must have been a folded colon, and distended the appendix. This organ could be plainly outlined by the bismuth in the lumen; it overhung the brim of the true pelvis, was long, and made a sharp bend near its middle. In the last plate of the series, taken 101 hours after the bismuth meal, the outline of the bismuth in the appendix could still be plainly seen. Four hours later, or nine hours after the ingestion of the bismuth, a most remarkable drop in the transverse colon occurred, making a large central loop reaching down into the true pelvis, and the hepatic flexure was one inch lower than in the previous picture (Fig. 3). Twenty-six hours after the bismuth had been taken, very little progress had been made, but the whole colon was distended with gas which collected in the upper parts and raised apparently the level of the hepatic flexure. The sigmoid flexure was outlined in places, and the colon retained the same shape as before. The eighth plate of this series, taken forty-eight hours after the bismuth meal, showed very little progress in the looped colon. The bismuth did not show in the descending colon, but filled fairly well the sigmoid flexure. Up to this time the patient had had no bowel movement; seventy-seven hours after the bismuth meal, the colon

retained its same position, but the main mass of the bismuth was still in the sigmoid flexure and the rectum. The sigmoid was very tortuous and long. The appendix was in the same position as before, and the same size. At the one hundred and first hour, without a movement, the bismuth was massed in the sigmoid and rectum and the appendix was still full of bismuth. It was two days after this picture was taken before the bismuth appeared in the stool, making a total of six days for the bismuth to pass through the gastro-intestinal tract. The diagnosis made in her case was a very severe case of constipation which, from the history, was probably the causative factor of the ptosed colon. At the time of writing, a laparotomy, with appendectomy and colopexy, is being considered.

CASE 2.—B. S., a girl 18 years old, shirt-waist maker, said that her mother had an ulcer of the stomach. For years the patient had had obstinate constipation and three years before she had been operated on for appendicitis and abscess formation. Since that operation the constipation had been growing worse, with headache across the temple, cramplike pains in the abdomen, worse at night, vertigo, heartburn, nausea, and occasional attacks of syncope which compelled her to give up work. She had no appetite and would vomit small amounts of food after eating; she said that she had vomited a tablespoonful of bright blood two weeks before examination by us in February, 1911. Her diet had been reduced to a ridiculously low amount, with nothing before lunch time. She had lost weight, but was still fairly well nourished. Her chief complaints were obstinate constipation, frequent vomiting, and pain in the epigastrium and back. Examination of the abdomen showed a good-sized scar over the appendiceal region, abdominal musculature was of good tone, and there was no distention. The outlines of the stomach seemed normal, but there was tenderness over the whole abdomen in general, which was localized over the epigastrium and along the spine, and more marked at the level of the tenth and eleventh dorsal vertebræ. The Ewald test meal showed a 0.07 per cent. and 0.04 per cent. free hydrochloric acid on two occasions respectively, with a total acidity within normal bounds. No lactic acid was present.

The diagnosis of an ulcer of the stomach as being the cause of her trouble seemed unlikely, no blood or occult blood being found in the gastric contents or stools. Lavage relieved her somewhat, but only temporarily. February 27, the bismuth Röntgen-ray test was applied. The first picture, taken fifteen minutes after the swallowing of the bismuth, showed a nearly normal stomach, oblique fish-hook type, which emptied rapidly.

The rugæ in the cardiac end were well marked. Within five hours the organ was completely empty. The small intestine was well down in the pelvic cavity.

The last picture in this series was taken twenty-four hours after the bismuth meal, and showed a ptosed cecum and splenic flexure. All the bismuth was in the large intestine, and the transverse portion of the colon has a long U-shaped loop, the lower border of which is 4 inches below the umbilicus, with its center 2 inches to the left of the median line. As this was one of our early cases, unfortunately we did not continue the series until the gastro-intestinal tract became completely empty. For a month and a half the patient was treated by regulation of the diet, massage and vibration, olive oil by mouth and per rectum, and by the usual instructions for regularity, etc., but an occasional cathartic was the only thing that gave her relief, and that only for a day or two. The flatulence, pain and vomiting continued. The pain now seemed localized over the left kidney with tenderness there, and an *æ*-ray picture showed absence of renal or other calculi. An exploratory laparotomy showed the long, looped and ptosed colon, which was distended with feces, in spite of previous catharsis and high enemas. One adhesion of the cecum to the abdominal wall, as the result of the appendectomy, was cut. The cecum was dilated but otherwise not pathologic.

Palpation of the stomach gave no evidence of ulcer or growth. The kidneys, gall-bladder and other organs seemed normal. The loop of the transverse colon was freely movable and low down in the pelvic cavity. With no permission to do a radical operation on the intestine, we closed the wound.

Since the operation the patient's condition has not improved, except for a short time after an abdominal web belt for the support of the ptosed colon was provided, and the patient sent to the country. At the end of last May she reported that the constipation was no better and that she still had attacks of sickness. She and her family have been advised of the probable necessity of a radical operation on the intestine, and of the dangers of the same, and have agreed to have it performed soon. We propose to sidetrack part of the colon, or possibly excise part of it.

## CONCLUSIONS

1. The length of time that it takes the contents of the gastro-intestinal tract to reach each division of the tract, and the time in which the division is completely emptied, can be definitely determined in each individual by the bismuth Röntgen-ray test.

2. The normal motility of each part of the gastro-intestinal tract can be definitely established.

3. The food immediately after ingestion begins to pass into the small intestine and by the end of an hour, at least one-quarter of the gastric contents is in the jejunum.

4. The stomach is emptied of 500 c.c. of milk or soup in two and one-half to four hours.

5. The existence of an increased amount of free hydrochloric acid in the gastric contents has no influence on the final emptying time of the stomach.

6. The time which this meal consumes in passing to the cecum averages two hours, varies from one to four hours, and is shorter in children.

7. The complete emptying time of the small intestine after this meal is probably about six hours.

8. Complete emptying of the colon consumes from twenty-four to forty-eight hours.

9. The bismuth-Röntgen-ray test is harmless and practical.

10. The ordinary methods of medical treatment can be more intelligently applied with the improvement in diagnosis accomplished by this test.

11. The bismuth-Röntgen-ray test should be employed before an operation is performed for a chronic condition of the gastro-intestinal tract.

We wish to thank Dr. George B. Wallace and Dr. John C. A. Gerster for their help in sending us patients, Dr. Arthur Mandel for his assistance in clinical and chemical analyses, and Dr. Alexander Smith, Dr. Egbert LeFevre and Dr. Harlow Brooks for their encouragement in undertaking the work.

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# EXPERIMENTAL INTESTINAL OBSTRUCTION

## REPORT OF FURTHER PHYSIOLOGIC, CYTOLOGIC AND CHEMICAL STUDIES *

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In general, those things which we see in mass are most certain to fix attention. The mucous lining of the dog's small intestine spread over 3 meters of tubular surface is more apt to be thought of in microscopic than in macroscopic terms. Possibly this is why certain of its functions relating to the animal economy may have been overlooked. Yet, in weight and, as some believe, in metabolic importance of secretions, it is the analogue of other great glands of the body. Its weight ratio to the thyroid is about as 7 to 1, and to the pancreas as 3 to 4. Its part in the balancing of metabolism has been overshadowed by its more obvious though measurably less important digestive function. It differs from other glands, not alone in its tesselated length, but in having a less free vascular interchange throughout its long course. What peculiar conditions as to function do these morphologic characteristics impose? If any, are they of significance in the perverted condition following intestinal obstruction?

On the other hand, take a spherical gland like the thyroid, for example; how are its cells activated to like function in like time? What more convenient method than by the interwoven blood-stream with its hormones and varying coefficients of osmotic pressure? How different seems the arrangement of the intestinal mucosa!

* From the Laboratory of Surgical Chemistry and Physiology, Rochester, Minn. Continuation of studies begun at Columbia University, New York, and reported before the Johns Hopkins Medical Society, March, 1909. (Am. Jour. Med. Sc., May, 1909.)

§ J. W. Draper Maury has taken the name John William Draper.

From these epithelial cells we know that the blood carries certain bodies which stimulate certain secretions.[1] This is a recently acquired habit and a highly specialized function, though older and less specialized than either sympathetic or central nerve control. Blood-stream messengers were doubtless used by our acardiac ancestors, for Draper[2] demonstrated nearly seventy years ago that hearts were a secondary contrivance and quite unnecessary to the maintenance of circulation. A more remote ancestral method of interglandular communication may have been the bathing of one pavement cell by the secretion of its next fellow. This method of stimulation in vertebrates is universally recognized in the activation of trypsinogen by enterokinase. Do not certain other substances follow the path of habit and of least resistance through the intestinal lumen? Surely, the experimental studies of Roger,[3] Matthews[4] and Pilcher[5] as well as our own, suggest this view. Furthermore, what other significance is to be attached to the terminal arrangement of the circulation in the small intestine? Free and lavish as is this blood-stream, its avowed architectural plan seems throughout the vertebrates merely for the purpose of hastening great volumes of blood to and from the intestine at the digestion period. Direct vascular interglandular communication appears minimized—definite lateral communication must have been provided had it been found functionally advantageous or necessary.

Embryologically, as Schulz[6] says, the analogues of the digestive tracts of the higher forms are first met with in mollusca. This relationship must not, however, be

1. Bayliss and Starling: Chemical Regulation of the Secretory Process, Proc. Roy. Soc., 1904, lxxiii, 310.
2. Draper, J. W.: The Chemistry of Plants. 1845, p. 37.
3. Roger, H.: L'occlusion intestinale, Presse méd., Jan. 4, 1911, p. 1.
4. Matthews, S. A.: One of the Functions of the Duodenum, THE JOURNAL A. M. A., July 23, 1910, p. 293.
5. Pilcher, J. T.: Cause and Relief of Pain in Duodenal Ulcer, Am. Jour. Med. Sc., 1911, cxli, 687.
6. Schulz, F. N.: Handbuch der Biochemie (Oppenheim), iii, Part 1, 228.

thought of as too close, because, among other things, so important an element as pepsin, for example, has not yet been positively identified in the invertebrates. It is significant, however, and germane to a study of obstruction that the great mid-gut gland of mollusks, although it contains glycocoll and is commonly looked on as liver, partakes at least as much of the nature of the vertebrate pancreas as of liver. Necessarily, being the chief organ both of assimilation and of digestion, it also functionally resembles our own highly specialized intestine. Originally there existed a free channel of communication between the cells of this gut-hepato-pancreas—a sort of general cellular washway. In vertebrates, however, a wide anatomic separation of the gland units (the liver and pancreas) with resulting ducts, has restricted the primitive method of cell-bathing to the intestine alone.

These abstract considerations are valuable because of their vital importance in every-day work. If we would seek for the cause and relief of human ailments, recourse must be had for intelligent hypotheses, not in purposeless leaps in the dark, but in the friendliest possible adaption of both our phylogenetic and ontogenetic evolution to experimental thought.

The belief that death in duodenal obstruction is caused by the actual interruption of enteric exchange thus seemed logical. What had been put together through untold ages of striving by millions of ancestral species could not without quick fatality be rudely set apart. Walter Cannon, in a personal note, justly complains that certain of us have too long looked on the alimentary canal as a highly ingenious contrivance of rubber tubes to be spliced and lopped at will. In the same connection, Pavlov[7] says, "The digestive process is a synthetic construction, all parts of the organism working together." The human animal in altruism and in intelligence surpasses all others. Physically, however, even among the invertebrates, as Schaler[8] says, man has many

7. Pavlov: Work of the Digestive Glands, p. 167.
8. Schaler, N. S.: The Individual, p. 126.

superiors. His glandular functions, as shown by Starling,[9] are as subject to the first-formed primitive influences as are those of any other vertebrate. How close is the relationship between biology and executive medicine! Finney's[10] conclusions as to the fundamental importance to surgery of a biochemical rather than a purely mechanical interpretation of the problems of gastro-intestinal perversions, are certainly pointed and timely.

It was not then by fortuitous guess that we began to feed the mucosa of the jejunum and ileum of one dog into the stomach and short intestinal segment of a duodenally obstructed dog. A reestablishment of the hypothetic simple signals of our primitive ancestors by putting together what the obstruction had taken apart should theoretically restore physiologic equilibrium and thus delay death. In a measurable degree this proved true.

Is there anything new under the sun? That the ancient Greeks attached a high sacrificial value to the entrails is humorously suggested by the following lines from Homer:[11]

> "They taste the entrails* and the altars load
> With smoking thighs."

This method of epithelial medication has in part answered the question suggested by earlier studies, "Does the intestine detoxicate by the addition of an anti-enzyme or does it save life by offering a larger field for absorption?" It is also germane to Bolognesi's[12] thoughtful studies on the chemistry of the blood in intestinal obstruction.

As in the case of delayed chloroform poisoning, the muscular twitchings spoken of by Howland[13] and

9. Bayliss and Starling: Uniformity of Pancreatic Mechanism of Vertebrata, Jour. Physiol., March 16, 1903, p. 174.
10. Finney, J. M. T.: Some Problems in Gastro-Intestinal Surgery, THE JOURNAL A. M. A., June 3, 1911, p. 1625.
11. Homer: Odyssey, Book iii, line 12.
* Presumably the liver and heart.
12. Bolognesi, Giuseppe: Recherches physico-chimiques du sang, dans l'occlusion intest. exp., Jour. de physiol. et path. gen., March 15, 1911, xiii, No. 2.
13. Howland and Richards: Jour. Exp. Med., 1909, ii, 344.

Whipple[14] were good clinical evidence of the degree of obstructive toxemia.

The posture which was due to the tonic spasms of the hind extremity muscles was frequently characteristic. So also was the carriage of the hind leg in walking. It

TABLE 1.—SERIES A; DOGS FED MUCOSA *

| NO. OF DOG | AVERAGE PULSE RATE | HRS. LIVED AFTER OBSTRUCTION | REMARKS |
|---|---|---|---|
| 6 | --- | 120 | First dog fed Mucosa;only moderately sick. |
| 8 | --- | 127 | Moderately sick. |
| 20 | 148 | 103 | Animal was a pup seemed resistant to toxemia,rapid emaciation. |
| 40 | 146 | 174 | Operated on at end of168 hrs.for gastro-enterostomy. death in 6 hrs. |
| 45 | 114 | 102 | Operated on at end of 96 hrs. for gastro-enterostomy. death in 6 hrs. |
| 49 | 160 | 120 | Pulse rose from normal to 180 in 15 hrs. Animal very toxic. |
| 63 | 144 | 127 | Peculiar condition:abduction of outer toe clonic spasms,rapid emaciation. |
| 72 | 123 | 163 | Operated on at end of 6th day for gastro-enterostomy. died in 19 hrs. |
| 75 | 140 | 180 | Mucosa stopped at end of nine days Spontaneous intestinal fistula. |
| 78 | 109 | 150 | Very marked muscular tremors. |
| 94 | 140 | 102 | Condition very good throughout. |
| 99 | 138 | 118 | Condition good up to last 24 hrs. when marked tremors began. |
| 112 | 128 | 57 | Very marked tremors.condition good. |
| 116 | 151 | 102 | No tremors but marked rigidity of hind-quarters. |
| 117 | 146 | 102 | Condition good but animal extremely weak. |
| 13 | 1787-15 | 1847 | |

137=Av.P.—123=Av.length-of-Life-when-fed-Mucosa;

* In several animals a late gastro-enterostomy was made in hope of saving life. Futile because too much toxemic damage had already been done.

is not unlike the swing of paraplegia in man. If death be due to glandular inactivation, the various coefficients of the pulse should afford reliable measures of the intoxication, for Rogers,[15] quoting Loeb, thinks that the

14. Whipple, G. H.: Chloroform Poisoning, Liver Necrosis and Repair, Johns Hopkins Hosp. Bull., xx, No. 222.
15. Rogers, C. G.: Am. Jour. Physiol., xxviii, No. 3.

heart-beat itself may be due to enzyme action. Adult dogs seem to have as unstable thermo-dynamics as young humans.

Hence, the rectal temperature has not appeared to be a reliable guide. It was usually but little changed by uncomplicated duodenal obstruction. Length of life, measured in hours after obstruction, obviously afforded the surest index of the efficacy of any form of treatment.

METHODS

Two series of fifteen dogs each have been prepared as follows: Under profound ether anesthesia in each case, the duodenum has been sectioned and infolded just aboral to the major pancreatic duct. All animals were treated exactly alike as regards dressings, postoperative care and free access to water. In Series A, however, each dog was given by mouth four times daily, about 30 c.c. of a watery suspension of mucous membrane scraped from the jejunum and ileum of healthy dogs which had been sacrificed by chloroform for the purpose. Approximately 400 c.c. of water were added to the entire scrapings and it was found that this suspension would keep on ice for about five days. No effort at standardization was made, but it was early observed that immediate treatment seemed more important than size of dose or later treatment.

One is tempted to speculate on the fate of numerous colon bacilli thus transplanted to unusual regions from the terminal ileum. Surgical introduction of such bacteria by implantation of a segment of the bacillus-bearing ileum into the duodenum had no visible clinical effect on two healthy dogs.

In this connection the brilliant work of Moraschi, Ruiz and Natale[16] of Buenos Ayres should not be forgotten. They have shown conclusively, by injection into rabbits, that the intestinal contents from the obstructed segment became less toxic directly as the obstruction neared the rectum. While the obstructed duodenal contents were the most toxic, the feces of the sigmoid were definitely the least toxic of all. This intoxication these

16. Moraschi, Ruiz, Natale: El proceso de la digestion y la toxicidad del contenido intestinal (Occlusiones experimentales hipotoxia fecal relativa), Sem. méd., Buenos Ayres, 1909, p. 1603.

authors would attribute to a symbiotic action of the bacteria.

This is a totally new conception, for prevailing opinion until recently has been that these bacteria themselves were the source of the fatal toxemia. The impression that we have gained, however, is that the bacteria were

TABLE 2.—SERIES B; DOGS NOT FED MUCOSA *

| No. of Dog | Average Pulse Rate | Hrs. Lived After Obstruction | Remarks |
|---|---|---|---|
| 1 | | 60 | Characteristic attitude of obstructed dog |
| 2 | | 72 | |
| 18 | 168 | 54 | Characteristic attitude. |
| 55 | 171 | 54 | Tremors, high pulse, rigidity very marked. |
| 57 | 175 | 126 | Pulse high and rapid, animal very resistant to toxemia. |
| 58 | 162 | 90 | Marked rigidity and rapid pulse. |
| 70 | 146 | 103 | Marked tremors, spasticity violent reaction 14 hrs. after operation. |
| 86 | 175 | 104 | Very high irregular pulse, marked tremors. |
| 87 | 161 | 78 | High pulse. condition excellent. walked up three stairs 12 hrs. before sudden death. |
| 88 | | 103 | Marked tremors of whole body. Too vicious to take pulse. |
| 89 | 194 | 54 | Extremely high pulse but no rigidity or tremors. |
| 90 | 194 | 30 | Very high pulse but did not appear sick. |
| 91 | 161 | 140 | A young pup, very resistant to toxemia. |
| 92 | 179 | 165 | Marked tremors but condition otherwise good. |
| 93 | 152 | 78 | Very powerful dog shows relation between vital and physical strength. |
| 12 | 2038-15 | 1311 | |
| | 170 Av. P. | 87 hrs. Av. length of life. | |

* The largest, strongest dogs were often the first to die. Physical strength no safeguard against obstructive autotoxemia.

facultative parasites and that at least the major part of detoxication was accomplished by the epithelial cells themselves. Orojejunal regions which bacterially are almost sterile have well defined power to limit the toxemia of obstruction.[17] It is not easy to see why this

17. Draper, Maury: Intestinal Obstruction. An Outline for Treatment Based on Cause of Death, Am. Jour. Med. Sc., May, 1909, cxxxvii, 725.

Fig. 1.—Animal in late hours of untreated duodenal obstruction. Posture is due to tonicity of hind leg muscles. Often walk on hind toes. Tendon reflex exaggerated.

Fig. 2.—Relaxed hind leg of duodenally obstructed dog. Note that toes are together. Hand grasping thigh, gently.

Fig. 3.—Spasm of leg shown in Figure 2, caused by pressure of fingers. This can be produced in normal dogs, but not so constantly. Toes separated.

primitive autogenous function, on the existence of which the interpretation of our provisional results is based, should have been relinquished by the cells most directly concerned, to be turned over to parasitic cells of alien species. It presupposes a true obligate symbiosis which is confessedly rare in nature.

There is another point; if these bacteria played so very important a part in intestinal metabolism, the giving of large doses of calomel, which Baumann[18] proved to have the power of suspending bacterial action,

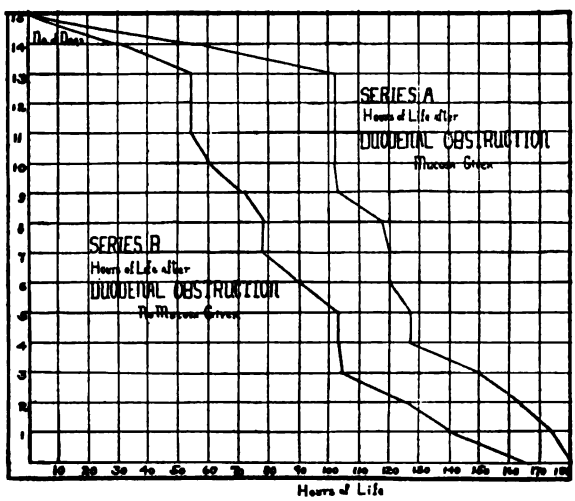


**Fig. 4.—Graphic chart showing that the effect of epithelial medication is noticeable during the first 100 hours only of obstruction. This fact and the parallelism of the subsequent charts strongly suggest a biologic reaction. Average difference in length of life between treated and untreated animals was thirty-six hours.**

should be followed by quite remarkable changes in the host. Ought not the healthy to fall sick and the obstructed to recover promptly? Still another point tending to refute the bacterial origin of the toxemia has been made by Frank Wood, who says (personal communication): "We not infrequently see cases of fecal

18. Baumann: Ztschr. f. physiol. Chemie, 1886, x, 123.

vomiting, in which, as soon as the obstruction is relieved, the patients recover promptly."

However this may be, those interested in the subject certainly owe a debt of gratitude to Roger and his pupils, who were the first to call our attention to the autogenous origin of obstructive toxemia. Whatever helpful parts the bacteria may or may not play, it is a healthful sign of progress that they have been relegated to minor positions in the consideration of death in duodenal obstruction. Emancipation is welcome from the hereditary text-book dogmas of "nervous influences," "shock,"

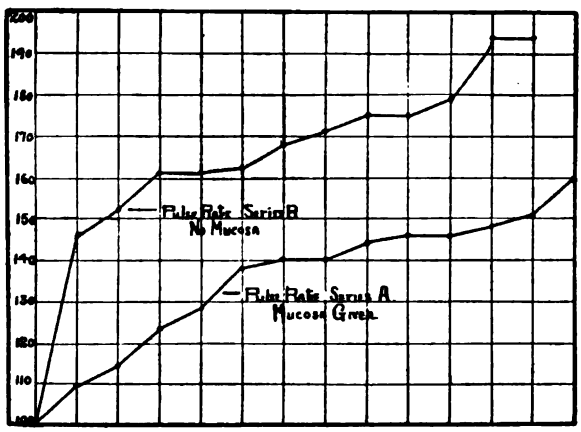


Fig. 5.—Graphic chart showing average pulse-rates in treated and untreated animals from operation until death. Note parallelism after initial separation of charts. Average lowering in pulse, 33 beats. Onset of high pulse usually within eighteen hours of operation. Too early for bacterial toxemia.

"stagnation of contents" and "passage of bacteria and bacterial products through the stretched intestine." These interesting symptoms should be set aside in favor of the underlying modern conception of glandular interaction, interference with which is probably the fundamental cause of obstructive death.

Jejunal and ileac mucosa, if capable of prolonging life and lowering the heart-beat in duodenally obstructed dogs, might reasonably be expected to modify any cellu-

lar tissue changes produced by the toxemia. One might expect such changes to be seen in the liver. So widely differing, however, is the morphology of the liver-cell under what appear to be normal conditions that we have as yet been unable to determine, with any degree of certainty, that duodenal obstruction caused any visible changes in the liver-cells. E. T. Bell[19] of the University of Minnesota has shown that the amount of fat present in a liver varied widely with the amount and quality of feeding.

How reliable an index of function, therefore, the presence or absence of morphologic changes in an organ might be after duodenal obstruction remains to be seen. Schlutz[20] has recently worked on a newly devised chemical method which Tollens[21] hopes may ultimately add to our knowledge of liver function. Dr. Schlutz suggested its possible usefulness in these studies, and I have the privilege of reporting his provisional findings.† The method deals with the quantitative determination of glycuronic acid. This substance combines with certain poisons, notably camphor, and this pairing or detoxicating is thought to take place entirely in the liver. By giving camphor hypodermatically, therefore, it seemed possible to find some true index of the functional condition of the liver before and after duodenal obstruction. In the single study of Schlutz completed to date the tables showed, first, that the nitrogen metabolism during camphor administration was well within the normal, both before and after duodenal obstruction; second, that the glycuronic camphor pairing decreased from 41 to 27 before and after obstruction. This may indicate that the liver function had been impaired.

19. Bell, E. T.: Anat. Rec., May, 1910, iv. Also article soon to be published in Internat. Monatschr.

20. Schlutz, F. W.: Die Fraction der Aminosauren im Säuglingsharn, Jahrb. f. Kinderh., lxxii, 97, 1910; Das Verhalten des Kamphers im Organismus des Säuglings, Ztschr. f. Kinderh., i, No. 2, p. 197.

21. Tollens: Ueber Glucoronsaure u. Aetherschwefelsauren im Menschlichen Harn., Ztschr. f. physiol. Chemie, 1910, lxvii.

† From the Laboratory of Physiology, University of Minnesota.

TABLE 3.—EXPERIMENT 1. DOG 30. EXCRETION OF NITROGEN *

| Date of Exp. | Length, Hours | Vol. of Urine c.c. | Total N gm. | Urea N gm. | Ammonia N gm. | Urea and $NH_3$ N gm. | Creatinin N gm. | Creatin N gm. | Creatinin and Creatin N gm. | Undeter. N gm. | Per Cent. of Total Nitrogen | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Urea | Ammonia | Urea and $NH_3$ | Creatinin | Creatin | Creatinin and Creatin | Undeter. N |
| 5/ 5 –6 | 23 | 520 | 13.60 | 10.4160 | 0.3998 | 10.8158 | 0.1830 | 0.2270 | 0.410 | 2.3472 | 76.58 | 2.20 | 78.78 | 1.346 | 1.670 | 3.014 | 18.205 |
| 5/ 6 –7 † | 25 | 460 | 15.40 | 11.060 | 0.580 | 11.640 | 0.210 | 0.280 | 0.490 | 3.270 | 71.81 | 3.76 | 75.57 | 1.364 | 1.819 | 3.182 | 21.248 |
| 5/ 7 –8 | 25 | 350 | 14.0 | 12.46 | 0.414 | 12.874 | 0.210 | 0.288 | 0.498 | 0.628 | 88.99 | 2.95 | 91.94 | 1.50 | 2.057 | 3.557 | 4.503 |
| 5/ 8 –9 | 18 | 282 | 12.40 | 11.08 | 0.340 | 11.420 | 0.137 | 0.333 | 0.470 | 0.5098 | 89.35 | 2.74 | 92.09 | 1.103 | 2.685 | 3.789 | 4.1214 |
| 5/ 9 –10‡ | 25 | 246 | 9.30 | 7.21 | 0.168 | 7.3780 | 0.1954 | 0.1298 | 0.3252 | 1.5968 | 77.52 | 1.8064 | 79.33 | 2.101 | 1.395 | 3.447 | 17.177 |
| 5/10–12§ | 47 | 325 | 12.20 | 9.10 | 0.680 | 9.780 | 0.2867 | 0.3318 | 0.6185 | 1.8015 | 74.59 | 5.5137 | 80.16 | 2.35 | 2.72 | 5.07 | 14.76 |

* Weight of this dog at beginning, 17 kg.; at end, ? † Five gm. camphor subcutaneously. ‡ Obstruction. § Cage—contaminated specimen. Vomitus mixed with blood and possibly urine or fecal matter. Total quantity, inc. wash water, 885 c.c.; total N, 6.797 gm.

TABLE 4.—GLYCURONIC ACID AND CAMPHOR-GLYCURONIC EXCRETION

Normal period = 1 c.c. of urine = 0.00081 gm. glycuronic acid.

| Date of Exper. | Length of Period, Hours | Volume of Urine c.c. | Nor. Amount of Glyc. Acid gm. | Amount Act. Passed as Comb. Camph. Glyc. Acid gm. | Increase Over Nor. gm. | Per Cent. of Theoretical Total Excreted in 48-Hour Period |
|---|---|---|---|---|---|---|
| 5/5–6 | 23 | 520 | 0.4222 | ..... | ..... | 5 gm. camphor = 11.20 gm. combined camphor-glycuronic acid. |
| 5/6–7 * | 25 | 460 | 0.3726 | 3.2195 | 2.8469 | |
| 5/7–8 | 25 | 350 | 0.2835 | 2.1144 | 1.8309 | Preceding obstruction: Total excretion for a period of 48 hours after giving camphor = 4.6778 gm. or 41.76 per cent. of a theoretical total of 11.20 gm. camph. glycuronic acid. |
| 5/8–9 | 18 | 282 | 0.2284 | 0.6144 | 0.3860 | |
| Operation | .. | ... | 0.8845 | 5.9483 | 5.0638 | |
| 5/9–10 | 25 | 246 | 0.1992 | 0.5904 | 0.3912 | Following obstruction: Total excretion for a period of 47 hours after giving 5⅛ gm. camphor =3.2498 or 27.19 per cent. of a theoretical total of 11.95 gm. camph. glyc. acid. |
| 5/10–12† | 47 | 325 | 0.2362 | 3.4860 | 3.2498 | |
| ..... | .. | ... | 0.4354 | 4.0764 | 3.6410 | |

* 5 gm. camphor subcutaneously. † 5⅛ gm. camphor at beginning of period.

## SUMMARY OF RESULTS

1. Epithelial cells of jejunum and ileum given by mouth to duodenally obstructed dogs prolonged life in a series of fifteen animals by about thirty-six hours over a similar series to which they were not given.

2. The average pulse-rate of the treated dogs was thirty-three beats lower than that of the untreated.

3. The belief that we were dealing with a cytologic product was strengthened by the trend of the charts. These showed that beneficial action occurred early, just as in the case of any successful treatment by antibodies.

4. The chemical determinations in one animal showed a normal nitrogen metabolism after duodenal obstruction and suggested a decreased functional power of the liver in terms of glycuronic camphor.

5. This series is far too small to justify any positive conclusions. Its value is simply that of a suggestive working basis.

# DISTURBANCES OF RESPIRATION DUE TO NUCLEAR AND INFRANUCLEAR DISEASE

C. F. HOOVER, M.D.
CLEVELAND, O.

Among what may be termed the triumphs of modern medical investigation, there are probably none more interesting historically or more illuminating in their results than investigations in external and internal respiration.

Although physiologists have greatly enlarged our views and knowledge of the subject, respiratory phenomena do not enlist the interest of clinical men so much as the growing knowledge of respiratory physiology warrants.

Physiology of respiration involves a number of problems, viz.: the lung as an areating organ, the mass movement of blood, the partial pressure of carbon dioxid and oxygen in alveolar air and circulating blood, products of metabolism and finally the nervous control of respiration which may be modified by alterations in the bulbar respiratory center cerebral cortex and pulmonary branches of the vagus.

I propose to describe some alterations in the nervous control of respiration which occur in several diseases we commonly see, tabes dorsalis, sclerosis of the brain arteries, tuberculosis of the mediastinal lymph glands and aneurysm of the first portion of the aorta.

Several years ago I read a paper before this Section in which were described some experiences with patients who had incipient tabes. These patients exhibited grave symptoms after receiving one-quarter of a grain of mor-

phin hypodermically. The patients suddenly lost consciousness and ceased breathing for twenty minutes. During this period of unconsciousness with suspension of respiration there was such pronounced vasomotor relaxation in the arteries of the extremities that there was a centripetal pulse in the veins of the hands which was distinctly visible and palpable. Artificial respiration was employed for twenty minutes when suddenly automatic respiration was resumed and with it consciousness returned, the arteries and veins both contracted and the centripetal venous pulse disappeared. At that time I made a careful search in literature to find some instances of death after small doses of morphin to see if some of these cases might not be of the character I described. None could be found in literature but after the publication of the article I received several communications from physicians who had seen such cases. One of them is of particular interest, as it ended fatally and suggests the probability of other unpublished cases. The case was reported to me by Dr. Poate of Black Creek, N. Y.

**The patient was a young man in the pre-ataxic stage of tabes who was given ¼ grain of morphin with 1/200 of sulphate of atropin on account of girdle pains. Forty minutes after the injection, the patient became unconscious and ceased breathing. The physician, who had left the house, was hastily summoned. Fully forty minutes elapsed from the time apnea and unconsciousness began until the physician was again in attendance. The patient's heart was still beating, but feebly and irregularly. Death occurred within a few minutes after the physician's return, so we can be sure the heart continued to beat for nearly three-quarters of an hour after respiration ceased.**

This is the only case I know of the kind which proved fatal but, as five cases were privately reported to me directly after the publication of my article in 1907, it seems probable that among the unreported cases there are some which ended fatally. My own two cases and four of those reported by other physicians regained their tolerance for morphin after the tabes made further progress. I mention this point at present as it has some

significance in common with other instances of apnea which have been ascribed to an elevation of the threshold of the respiratory center. I have seen several patients with cardiovascular disease who were greatly distressed with slumber apnea and waking hyperpnea early in the progress of their disease before air hunger from vigorous exercise during the waking hours made its appearance. And yet these same patients were not disturbed by slumber apnea a year later when the slightest muscular exercise was followed by distressing air hunger.

Some patients with cardiovascular disease develop Cheyne-Stokes breathing after a moderate dose of morphin. Other patients who suffer from Cheyne-Stokes breathing during their waking hours, or have their rest disturbed by slumber apnea and waking air hunger, seem to suffer less from the symptoms we associate with a high threshold of their respiratory center after the administration of morphin. This is contrary to our expectation if we are dealing purely with the sensitiveness of the respiratory center to the partial pressure of carbon dioxid and oxygen in the arterial blood. It is a common experience to see a patient with arteriosclerosis develop Cheyne-Stokes breathing immediately after a hemiplegia from arterial thrombosis develops and then recover from all respiratory symptoms as he recovers from his hemiplegia. Yet during all these periods there will not be the slightest indication of any change in the mass movement of blood.

A few years ago I saw a man 65 years old who had marked arteriosclerosis with a high blood-pressure, great cardiac enlargement and anasarca, whose chief distress was alternating apnea and hyperpnea. During the apneic periods, which lasted from thirty-five to fifty seconds, he became drowsy and when he was urged during the apnea to take a breath he would turn his head from side to side and make an ineffectual effort to breathe. He would lift the thoracic cage but did not open the glottis, as was apparent by the retraction in the suprasternal notch and the epigastrium and the absence of a respiratory murmur when the stethoscope was applied over the trachea. This man recovered from his Cheyne-Stokes

**respiration after the liberal use of nitroglycerin and caffein, although the anasarca was unchanged and the disease ended fatally two weeks later.**

The slumber apnea seems to be associated with a light sleep in many instances, whereas, a deep sleep is undisturbed. All of these facts point to some influence on the respiratory center from the cerebral cortex. So it looks as though we are in many instances dealing with something more than an altered bulbar respiratory center.

During the past year Dr. J. J. R. Macleod and I have been making a series of observations on a patient with cardiopulmonary disease who is persistently cyanotic without dyspnea and in whom the alveolar air shows a content of carbon dioxid which ranges from 7 to 9 per cent., a percentage which no man in health can endure, yet this man always developed apnea from ten to twenty seconds as he would go into a doze while we were taking tracings of his respiratory movements in a pneumograph.

Unverricht[1] made similar observations in studying the relative effects of morphin and atropin on respiration. He saw some patients who lost their Cheyne-Stokes respiration after morphin was given. Unverricht thinks the periodic breathing sustains a certain relation to cortex excitation, as some of his patients had periodic breathing during light sleep and lost their periods of apnea in profound sleep. Unverricht says that in his animal experiments when sleep was induced by morphin or chloral a mild degree of narcosis was associated with Cheyne-Stokes breathing, but a larger dose of the drug caused the Cheyne-Stokes breathing to cease. He also mentions the fact that he has seen Cheyne-Stokes respiration appear in an animal from the mere procedure of exposing the brain.

That degeneration of the vagal nuclei play an essential rôle in apnea is well supported by pathologic evidences. But the kind of disturbances is not always the same. The case of paretic tabes reported by Egger[2] had per-

1. Unverricht: Centralbl. f. klin. Med., Supplement, p. 55, 1892.
2. Egger: Jour. d. physiol. et path. gen., 1899, i, 68.

sistent bradypnea (6 per minute) and would have apnea for one minute followed by three respirations during the second minute directly after a dozen deep respirations were rapidly taken. There was then a period of short apnea like the "hunting" of the respiratory center as described by Haldane. There was no alteration of apnea with hyperpnea when the patient was left to spontaneous respiration. That there was a heightened threshold to the respiratory center is apparent from the persistent bradypnea, and further reduction of the respiratory rate after the carbon dioxid was washed out of the blood by forced breathing. But that is a much simpler phenomenon than Cheyne-Stokes respiration in patients with arterial disease. And it also differs from the phenomenon of "hunting" after apnea has been induced in healthy subjects by prolonged forced breathing.

In the tabetic cases, we are dealing with a process which is limited to the bulbar nuclei and is not associated with disturbances in the higher cerebral structures, as we know occurs in arteriosclerosis and may play a part in experiments of forced breathing in healthy subjects.

Two cases of Cheyne-Stokes breathing from arterial disease are reported in Guys Hospital Reports.[3] Both patients were examined pathologically by Buzzard who reported hemorrhages and marked nuclear degeneration in the dorsal nuclei of the vagus. Both these patients had high arterial pressure, cardiac hypertrophy and hemiplegia. In both patients the Cheyne-Stokes breathing was changed to a normal rhythm when oxygen was inhaled by using a mask but not when the oxygen was given through a funnel suspended over the face as oxygen is usually given. In my own experience, two such patients with hemiplegia changed from a pronounced Cheyne-Stokes to a normal respiratory rhythm when a good stream of oxygen was given through a suspended

3. Pembrey: Guy's Hospital Reports, lxi, 25.

funnel. The change was very prompt. If we started the oxygen in the middle of the hyperneic period the succeeding apnea was abolished. From the physiology of external respiration we can understand how promptly the partial pressure of oxygen may be raised in the arterial blood and thus lower the threshold of the respiratory center. But this explanation either includes only a part of the process involved or different diseases of the respiratory center give varying respiratory symptoms. The changes of the respiratory rhythm which have been ascribed to some modification of the respiratory center cannot be explained purely from independent and reciprocal changes in the partial pressure of oxygen and carbon dioxid, so Haldane and Zuntz have offered the presence of lactic acid (which forms under deficient oxidation of tissues) as a third factor in causation of altered respiratory rhythm from deficient oxidation of the respiratory center. Possibly we may learn that deficient oxidation of the center and partial degeneration of the center will give different symptoms, but there remains much to be done in the way of clinical observation, physiologic experiment and pathologic studies before we can assign certain symptoms to physiologic and other symptoms to anatomic changes in the bulbar centers.

Enough has been shown, however, to clinch several practical points, viz.: (1) that the use of respiratory depressants must be employed with great caution when there is any reason for suspecting an anatomic degeneration in the respiratory center, and (2) that the use of oxygen inhalation will restore the normal respiratory rhythm when alternating apnea and hyperpnea are caused by deficient oxidation of the blood, as in mountain sickness, or when the same altered rhythm is associated with arterial disease. Thus far I have tried to show that impulses from the cerebral cortex may share in the respiratory symptoms which we have been in the

habit of ascribing solely to changes in the bulbar respiratory center.

I now wish to describe some instances of disturbed respiration which originate from disturbed peripheral innervation of the lung. Symptoms may arise in several ways from this source. There may be a neuromuscular reaction as evidenced by spasm of the bronchioles resulting in pulmonary emphysema with great distress in breathing, i. e., genuine dyspnea attended with cyanosis from deficient lung ventilation, or the patient may have tachypnea without cyanosis and without impaired lung ventilation and without genuine air-hunger, although the respiratory distress is very severe.

The first instance of emphysema from this source I wish to describe was in a little girl 6 years old who had recurring attacks of emphysema from caseous tuberculous glands of the mediastinum. This child formerly had a chain of suppurating tuberculous glands on each side of the neck from which the scars were very conspicuous along the anterior border of each sternomastoid muscle. For the year preceding the time I was called to see the child she had been having attacks of asthma, which would come on with great suddenness, last about half an hour and then cease as suddenly as they began. The attacks occurred only once in two or three months. During the remaining time the child was regarded as being quite comfortable, although she was recognized as poorly developed and without much endurance.

As I saw the child she was cyanotic and extremely dyspneic. The dyspnea was expiratory and percussion showed that the lungs filled the pleural sinuses. The pulse-rate was 120 and the heart was not dilated. In the midst of a respiratory phase, all traces of respiratory distress ceased so that within a few seconds there was a transformation from great distress to complete respiratory comfort. The lower borders of both lungs ascended three fingers' breadth and all sibilant râles disappeared. This transformation was so sudden that it could not have occurred in any other way than from some neuromuscular activity.

That vagus excitation can cause spasm of the bronchial muscles and thus cause emphysema was clearly shown by Einthoven's[4] experiments which were con-

4. Einthoven: Arch. f. d. ges. Physiol. (Pflüger's), 1892, li, 367.

firmed later by several observers who employed Einthoven's methods.

After the emphysema subsided in this child the pulse-rate remained the same (120) and the patient remained absolutely at rest without any sign of discomfort. About thirty minutes after the emphysema subsided, death suddenly occurred without a moment's warning. At the autopsy, the mediastinum was found completely filled with caseous tuberculous glands. Both vagi were included in the midst of this inflammatory mass. Although the vagi were not examined histologically the gross pathology and the character of the symptoms justify a diagnosis of vagus neuritis.

Another case of similar character occurred at Lakeside Hospital two years ago, in a man who had an aneurysm of the arch of the aorta. Both vagi were firmly embedded in the periaortic tissue and showed by staining of a cross-section that there was marked atrophy of the nerve elements in both nerves. This man gave a history of cough with dyspnea on exertion. But until the day before he was brought to the hospital there had never been any severe respiratory symptoms. The dyspnea came on suddenly and with great severity, so that the attending physician described his patient as suffocating.

Physical examination revealed some striking inconsistencies. The patient was extremely dyspneic but the only assignable cause for dyspnea was a moderate pulmonary emphysema. There was no pulmonary edema and no signs of bronchitis beyond those which accompany the usual acute bronchial asthma. There were no evidences of a severe disturbance in the mass movement of blood, such as dilated jugular veins, engorged liver or edema. The systolic and diastolic arterial pressure and the excursion of the arterial wall were consistent with a good systolic output of the ventricle. The heart-rate was 120. It was, however, quite apparent that the man was suffering from an impairment of external respiration far greater than could be accounted for by the cardiovascular or pulmonary signs.

During the physical examination the area over the manubrium was found quite dull and gave a distinct tracheal tone with gentle percussion. Our interpretation of the case was mediastinal tumor with vagus disease. The patient died two hours after admission to the wards. The autopsy revealed an aneurysm of the ascending arch as large as a man's fist. Both vagi showed the gross and histologic evidences briefly described.

It is true the man had an aneurysm, but aneurysm did not cause his death. Death was due to vagus disease. The antemortem diagnosis of tumor with vagus neuritis was a correct physiologic diagnosis but anatomically it was wrong.

Atropin sulphate 1/50 grain was given subcutaneously but did not affect the pulse-rate nor the emphysema.

At autopsy the lungs did not reveal the slightest signs of atrophic emphysema nor any other disease—a fact which confirmed the diagnosis of vagus emphysema.

It was unfortunate that oxygen was not given in this case, as its results would have some bearing on the relations between the vagi and the absorption of oxygen from the alveolar air. I think this is of importance in view of the difference of opinion which exists among physiologists as to whether the absorption of oxygen by the blood from the alveolar air is a purely physical or partly a so-called vital process. So far as my own observations go, dyspnea and cyanosis from vagus disease are intimately linked with a neuromuscular pulmonary emphysema.

The two following cases had no emphysema nor cyanosis nor extreme air-hunger, all of which characterized the two preceding cases of vagus disease. They had, however, extreme respiratory distress of quite a different character.

The first patient of this kind was admitted to Lakeside Hospital Oct. 21, 1910. He was brought to the accident ward with acute cardiac dilatation and pulmonary edema and extreme dyspnea. On entrance he was bled 20 ounces and 1 milligram of strophanthin was given intravenously.

Twelve hours later, when I first saw the patient, he was very comfortable. His personal history contained an account of an attack of articular rheumatism seven years before, since which time his physical endurance had been impaired. There was also a doubtful history of a syphilitic infection prior to the attack of rheumatism. The heart's area of dulness extended 15 cm. to the left of the median line in the sixth intercostal space and the right precordial border was 5 cm. to the right of the median line in the fourth interspace. The aortic area of dulness was 5 cm. to the right of the sternum at the right second interspace. The maximum systolic pressure in the artery was 152. The diastolic pressure was very low and the auscultatory signs confirmed an insufficiency of the aortic valves.

A skiagram showed a marked dilatation of the first portion of the arch of the aorta, which was the most essential pathologic lesion in this patient.

After the patient had been one week in the hospital and seemed comparatively comfortable, he began having attacks of dyspnea which lasted from a few minutes to several hours. The resident physician gave him injections of morphin (when the attacks were prolonged) but after a few days the attacks came more frequently and the morphin gave him unsatisfactory relief. These attacks of dyspnea occurred between November 5 and 15, i. e., from the sixth to the fifteenth day after admission to the ward.

November 15, the patient had an attack during the ward visit while we were making some observations on his condition. The man was breathing twenty times a minute and had a pulse-rate of 80. While I had my finger on his pulse the rate suddenly dropped to 40 per minute. By the time the new rate of 40 had progressed for about four cardiac cycles, very rapid breathing commenced. The rate of respiration was suddenly increased to 60 per minute. The patient had a tachypnea and not a hyperpnea. The thorax never attained the expiratory phase. The excursion of the thorax was always far above the abscissa. During the bradycardia with tachypnea, the blood-pressure, systolic and diastolic, remained unchanged. There was no change in the volume of the heart. The jugular veins were not dilated nor did their pulsations change and there were no signs in the lung nor in the heart to suggest pulmonary stasis. There was no cyanosis. The patient did not offer any sign to suggest an impairment of the mass movement of blood nor any transient change in the lung or bronchioles to impair the lung as an areating organ. Indeed, it was particularly noted there were no evidences present which we associate with emphysema.

When the patient was asked if he was short of breath his reply was "yes." "But do you feel air hunger as one experiences after a long hard run?" was asked. "No," was the patient's reply, "I feel very much distressed and a strange feeling of pressure seems to strike me here (pointing to the midsternal region) which compels me to breathe rapidly."

The paroxysm of bradycardia naturally suggested the use of atropin. We were gratified to find the bradycardia and tachypnea would both subside in ten minutes after the hypodermic injection of 1/100 grain of atropin sulphate. This was given routinely morning and evening, after which treatment there was no return of the paroxysms. The patient had relief by atropin from several paroxysms before the routine treatment was adopted.

That bradycardia of vagal origin should be relieved by atropin is familiar enough, but why should tachypnea be arrested by atropin? I find in a report of S. Baglioni[5] which has an interesting bearing on this experience. Baglioni discusses the experiences of his predecessors in experimenting on the pulmonary branch of the vagus, all of which seemed to prove that excitation of the pulmonary vagus branch had two effects: one was to arrest the heart-beat more promptly and with a lesser stimulus than when the central end of the vagus trunk was excited, and the other effect was an arrest of respiration.

Baglioni, however, found that what was regarded as apnea was in reality a very rapid tachypnea which played high above the abscissa in the tracings. In reviewing the tracings made by his predecessors he calls attention to the very significant fact that their tracings show apnea during the inspiratory phase whereas apnea always occurs in the complete expiratory phase.

In this patient we have an anatomic lesion, i. e., aneurysm of the first portion of the arch of the aorta which is very favorable for excitation of the pulmonary branch of the vagus. The tachypnea (without air hunger or circulatory or pulmonary impairment) came on coincidently with bradycardia and both were relieved by atropin in ten minutes after hypodermic injection.

March 11, 1911, we received another patient in the woman's ward who confirmed the experience above described in a very interesting way. The patient was 43 years old. She gave a history of syphilis, the physical signs and skiagram revealed an aneurysm of the first portion of the arch of the aorta.

After the patient recovered from very severe symptoms which led to her being brought to the hospital, she commenced to have paroxysms of tachypnea. The respiratory rate was usually from 18 to 20 per minute. The attacks of tachypnea would come on with great suddenness without cyanosis or any signs of cardiac or pulmonary impairment, and unlike the former case, the tachypnea was not associated with any change in the heart-rate.

The description of the attacks which was recorded by Dr. Taylor (resident physician) is particularly interesting, as it

5. Baglioni, S.: Arch. Ital. de biol., 1909, lii, 236.

accords so well with Baglioni's account of the results from excitation of the pulmonary branch of the vagus. February 15, four days after admission, the notes read as follows:

"Patient had a second attack of tachypnea this evening. When first seen the respiration was 36 per minute and the heart-rate 88. The air hunger consists in an inability to get rid of her air. She would take a deep inspiration and then hold it, at the same time giving the impression of numerous small respiratory efforts at the height of the inspiratory phase. Then with extreme effort, using all the muscles of expiration, she would expel the air from her lungs, only to take another deep inspiration and repeat the performance."

Atropin, 1/50 of a grain, relieved the distress in ten minutes. This patient had three such attacks which were relieved in ten minutes by atropin.

I have been able to find only one reported case which is like these last two described cases. Pal[6] describes the case of a young man with severe mitral stenosis in whom frequent attacks of tachypnea occurred. The respiratory rate would vary from 50 to 120 per minute. Inhalations of oxygen gave no relief. Pal says nothing about the use of atropin. His patient had tachypnea without slowing of the heart-rate. At the autopsy, Pal found the left vagus, at the hilus of the lung, was imbedded in a mass of enlarged lymph glands. The vagus was much thickened in this location. Unfortunately, through some misadventure, the specimen was spoiled so that no histologic examination of the nerve could be made.

1903 E. Seventy-Fifth Street.

## ABSTRACT OF DISCUSSION

DR. YANDELL HENDERSON, New Haven, Conn.: So far as I know this is the first paper on the subject ever presented in America. During the past five years there has been an immense amount of interest shown by clinicians in the study of the circulation. The clinical aspects of arterial pressure have been studied especially by the methods of the physiologic laboratory. But a similar study by precise methods of the equally important subject of the clinical aspects of respiration has been neglected. Dr. Hoover's paper is the first step into this rich and important, yet unworked, field of clinical investigation.

One of the important points to be kept in mind is the fact that recent progress in physiology has shown that lack of oxy-

6. Pal: Wien. klin. Wchnschr., 1906, Nos. 47 and 48.

gen is not a direct stimulus to respiration. It is not a lack of oxygen which causes us to breathe but the driving force of the carbon dioxid which is circulating in the blood. If the tension of carbon dioxid falls, there is a cessation of respiration until the reaccumulation of the necessary amount of carbon dioxid in the circulating blood again stimulates the center. In conditions of hyperpnea during and after muscular exercise, carbon dioxid, not oxygen, is the regulating factor of the amount of air that enters and leaves the lungs per minute.

There is, however, a complex reflex mechanism also involved in respiration. It determines the form of breathing—whether the breaths shall be shallow and rapid, or deep and slow. This reflex mechanism is similar to that which controls the finer movements of the legs in walking. Some of the disturbances of respiration which Dr. Hoover has described are clearly ataxic. They are wholly analogous to the phenomena of locomotor ataxia. It is interesting to notice, as Dr. Hoover has pointed out, that syphilis causes the same type of disturbances of respiration as of walking.

Another point to which especial attention should be called in connection with Dr. Hoover's observations is that Cheyne-Stokes respiration is really not a pathologic phenomenon. It is frequently met with in perfectly healthy human beings. The majority of healthy persons can readily induce in themselves a period of intermittent breathing; a couple of minutes of voluntary forced breathing is usually sufficient to start it. I have repeatedly noticed in healthy individuals, who have lain down to take a nap after a hearty meal, that this type of breathing comes on. During one of the apneic pauses the person will suddenly start in his sleep and become wide awake. This, I think, is essentially the same phenomenon as the sudden terrified awakening of Dr. Hoover's patients. They feel that they have stopped breathing. If the apneic stage has been prolonged the dyspnea would, of course, be proportionately violent. The probably explanation of this is that in such patients as Dr. Hoover has described the sensitiveness of the respiratory center is subnormal. It is probably further reduced below normal as the subject falls asleep. Accordingly the amount of carbon dioxid in the blood is insufficient to maintain breathing. The subject therefore stops breathing until half asphyxiated for lack of oxygen; then he suddenly awakes. For the relief of this condition I would suggest that before the patient tries to go to sleep a paper bag, or a mask connected with an open tube of some length (say a piece of bicycle tire for example) should be held over the patient's face. Under these conditions a slightly excessive amount of carbon dioxid will accumulate in the person's lungs and blood. This amount would probably be sufficient to keep the respiratory center at work when the subject falls asleep. The occurrence of apnea and the terrified awakening would thus be prevented. Dr. Hoover's paper is certainly a valuable contribution to the physiology of respiration.

# THE SIMULTANEOUS AND CYCLIC APPEARANCE OF EPIDEMICS OF PNEUMONIA, GRIP AND ENTERITIS ON THE NORTHERN HEMISPHERE

## AND THEIR SYNCHRONISM WITH SOLAR ACTIVITY CYCLES

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SAN FRANCISCO

Before this Section in 1894, I read a paper on the influence of atmospheric pressure conditions on the prevalence of pneumonia,[1] and I published a further study on this subject in 1908.[2] My conclusions, based on my former research and with special reference to epidemics of pneumonia in Chicago and San Francisco during the five years, 1899 to 1904, I formulated thus:

Pneumonia is not merely a concomitant of the cold weather season. Its prevalence depends on anticyclonic weather, summer and winter, on the northern hemisphere, and not on low temperature. There is sufficient reason to assume that the quality of the air of an anticyclone changes in conformity with changes in the activity of the sun and that the prevalence of grip and pneumonia is subject to a specific quality of such air.

In support of these conclusions, I prepared charts† showing: first, the even temperature and humidity line of San Francisco, the number of hours of sunshine and the amount of rain for every day of the eleven years, 1888-1899, where obtainable, in contrast to lines of pneumonia and bronchitis mortality per week and the air-pressure extremes of every day; second, similar data

1. Richter, C. M.: THE JOURNAL A. M. A., Aug. 4, 1894, p. 188.
2. Richter, C. M.: THE JOURNAL A. M. A., Aug. 22, 1908, p. 660.

† These charts were on exhibition at the Los Angeles Session, in the Scientific Exhibit.

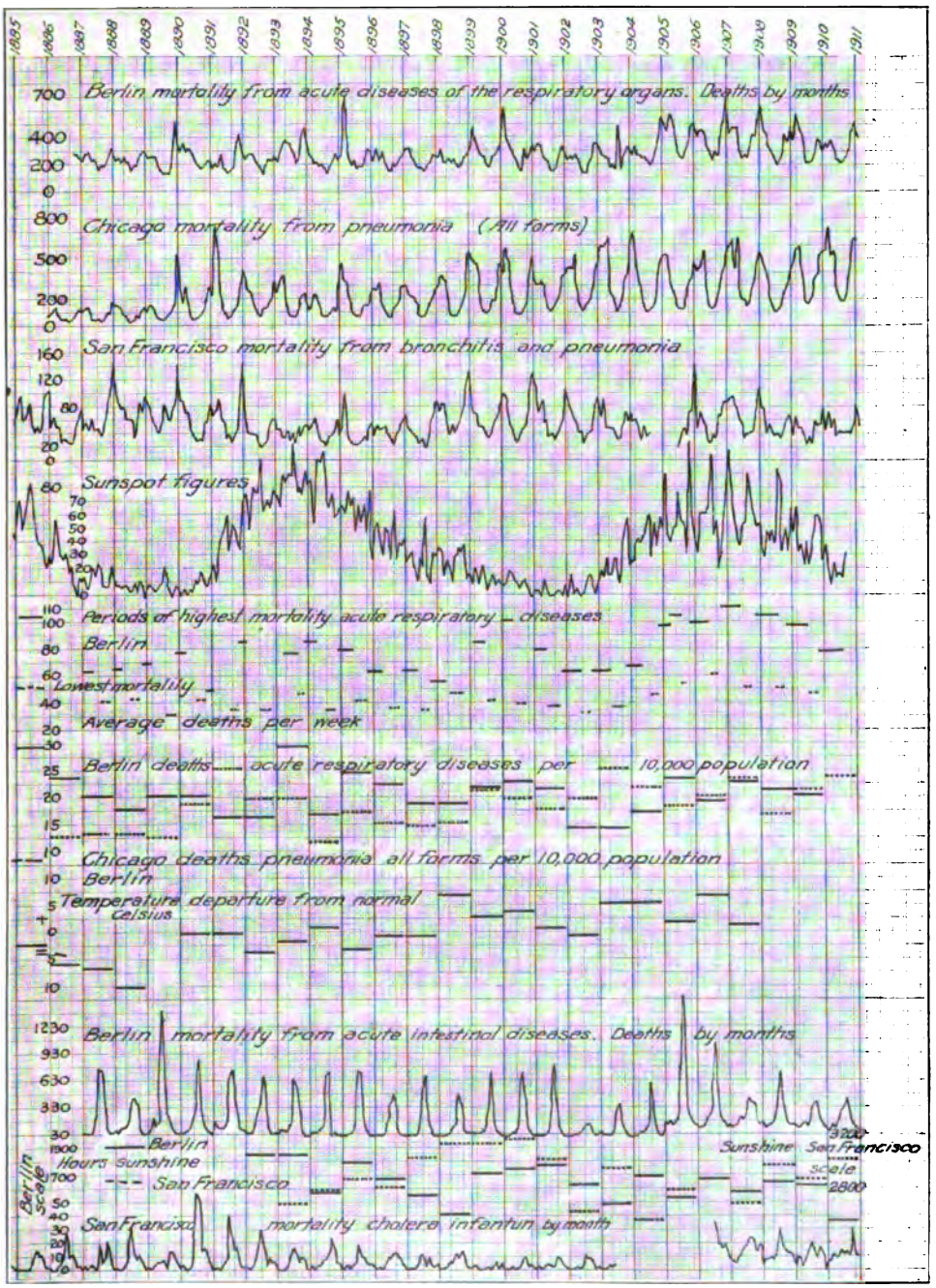
1885 1886 1887 1888 1889 1890 1891 1892 1893 1894 1895 1896 1897 1898 1899 1900 1901 1902 1903 1904 1905 1906 1907 1908 1909 1910 1911
Berlin mortality from acute diseases of the respiratory organs. Deaths by months
Chicago mortality from pneumonia (All forms)
San Francisco mortality from bronchitis and pneumonia
Sunspot figures
Periods of highest mortality acute respiratory diseases
Berlin
Lowest mortality
Average deaths per week
Berlin deaths acute respiratory diseases per 10,000 population
Chicago deaths pneumonia all forms per 10,000 population
Berlin
Temperature departure from normal
Celsius
Berlin mortality from acute intestinal diseases. Deaths by months
Berlin
Hours Sunshine
San Francisco
Sunshine San Francisco scale
Berlin scale
San Francisco mortality cholera infantum by month

**Chart 1.**—Epidemics of pneumonia and enteritis in Berlin, Chicago and San Francisco.

during the time of grip and pneumonia epidemics at Berlin and New Orleans in the winter of 1889-90; and third, charts giving the weekly pneumonia mortality and the daily air-pressure observed at Chicago and San Francisco during the five years, 1899 to 1904.

I emphasized in my last paper that "any investigation of this nature should not be limited to proving a reciprocal relation of certain weather conditions and pneumonia and grip as existing in a city or on a small part of our globe, but should be carried on to prove such relation for at least one hemisphere." In consequence, I studied this subject in reference to Berlin, as the figures published weekly by the Imperial Health Office of Germany give ample material for such study. I prepared two charts in relation to this research, each covering the twenty-four years from 1887 to 1911, showing the weekly mortality from acute respiratory diseases, the daily extremes of air-pressure, temperature and relative humidity, the figures of rain, of sunshine, of the sunspots observed on every day, and the weekly mortality from acute gastro-intestinal diseases. The wind direction is given for the periods of epidemics.

For convenience, I use in this paper and on the charts, when not otherwise stated, the word "pneumonia" to represent acute respiratory diseases, and the word "enteritis" to represent acute gastro-intestinal diseases.

I learned from these charts the following facts for Berlin: The prevalence of pneumonia depends, as at Chicago and San Francisco, on anticyclonic weather, summer and winter, and not on sunshine, temperature, or relative humidity.

The period of lowest mortality from pneumonia is always synchronous with relative absence of anticyclonic weather and with the appearance and development of enteritis epidemics.

Enteritis and cholera infantum epidemics (under 1 year) at Berlin do not last many weeks. They generally have a rapid rise and fall. They either precede

the period of lowest air-pressure during the summer for a few weeks, or more often are simultaneous with it.

Cholera infantum figures (under 1 year) in these epidemics, represent uniformly about 60 per cent. of the total number of enteritis cases.

The United States Census Mortality Report for 1908 gives a ratio of 80 to 85 per cent. of deaths from enteritis and diarrhea to children under 2 years in the United States. Convulsions under 5 years would add 1 to 2 per cent. to this figure. The Chicago figures include "convulsions" since 1908.

This group of gastro-intestinal diseases at Berlin appears in an epidemic form during the periods of the extreme heat of the summer, but not in proportion to the extent, or to any distinct quality of such periods. Positive or negative departure from normal temperature during the twenty-four summers does not modify their appearance in a fundamental way. The amount of sunshine and the degree of relative humidity possess no causal relation; but an absence of anticyclonic weather is very conspicuous during such an epidemic.

San Francisco is practically immune from cholera infantum and from enteritis epidemics in general. The high summer heat is wanting here, but whenever spells of extreme heat have occurred, they were not followed by a prevalence of enteritis. However, we find during a San Francisco summer a relatively high air-pressure condition, very different from the period of "low" observed at Chicago and Berlin. (For similar reasons San Francisco suffers more from pneumonia during the summer months, than the two cities named.)

The anticyclonic weather, of course, should not be judged merely by high pressure figures, but by the direction of wind as well, and this should indicate that the air in question is an outflow of an anticyclone. For it is more the quality of the air brought to us by an anticyclone than its numeric value that we consider.

"It is not the absolute height of the barometer that is determinative in locating anticyclones, but rather the relative height of the barometer compared with that of the surrounding districts."[3]

For practical considerations, we may assume that air-pressure fluctuations of 20 to 30 mm. will not affect our organism materially, except its most elastic tissues—the lungs and the soft abdomen. A reduction of air-pressure of 30 mm. signifies a loss of weight of 80 kilos on the abdominal surface.

A maximum of air-pressure brings at the same time the highest amount of oxygen into the lungs. It has been proved, experimentally, that an excess of oxygen inhaled may cause pneumonia.

Considering the importance of the quality of air we breathe under different atmospheric conditions, I directed the next step of my research to an inquiry into the influence of solar activity on weather conditions, principally on air-pressure fluctuations.

Chart 1 points out epidemics of pneumonia and enteritis by the monthly mortality figures of Berlin, Chicago and San Francisco. It will be recognized at once that the cities have their pneumonia epidemics during the same years or period of years and that especially the last sunspot period seems to cover a prevalence of pneumonia during its cycle.

On the same chart will be found the lines of periods of highest and lowest pneumonia mortality for Berlin, these lines indicating the average weekly mortality during such periods. These periods cover from one to five months at ever changing parts of the seasons, but were always found to be in direct dependence on anticyclonic conditions.

The mortality figures are given as well at the scale of 1:10,000 population, to give proper estimate of the real mortality. Besides, there are the yearly departures from

3. Symons, I. Hann: Meteor. Mag., April, 1911.

normal temperature and the yearly sunshine values for Berlin, the latter also for San Francisco.

The different scale for the hours of sunshine points to the fundamental difference between Berlin and San Francisco in this respect. All figures are generally for the twenty-four years ending December, 1910.

Chart 2 exhibits the direct dependence of air-pressure conditions on solar activity (judging from sunspot figures) for eighty years (1830-1911) more or less, and for the cities of St. Petersburg, Berlin, Paris, Triest and Palermo in Europe; Boston, Philadelphia, Cincinnati, Chicago and San Francisco in America.

F. H. Bigelow[4] says:

> The response to a change in the solar energy, when recovered at the earth, is by no means simple. We are guided in this respect by the prominences and sunspots and we consider them as products of the outgoing radiant energy.

Sunspots have a varying period of from 11.1 years to 13.3 years. Besides, there is the constantly changing area of the sun, which is covered by spots. This area amounted to a minimum before the grip epidemics of 1835 and 1889.

On a purely mathematical basis, A. Schuster[5] found periods of solar activity that amount to 4.8, 8.4 and 11.1 years.

These periods may cover, as he says, a period of 33.4 years.

F. H. Bigelow adopts a 33-year mean and subdivides it by 3- to 4-year periods. He concludes that "the magnetic field variations (of our earth) are one result of the absorption of the incoming radiation in the earth's atmosphere and the temperature changes are another product of it, linked up with the circulation and thence with the barometric pressure and weather conditions generally."

I demonstrated this correlation of air-pressure and sunspot periods in 1892.[6]

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4. Bigelow, F. H.: Am. Jour. Sc., August, 1910.
5. Schuster, A.: Proc. Roy. Soc., 1905, lxxvii.
6. Richter, C. M.: Meteor. Ztschr., August, 1892.

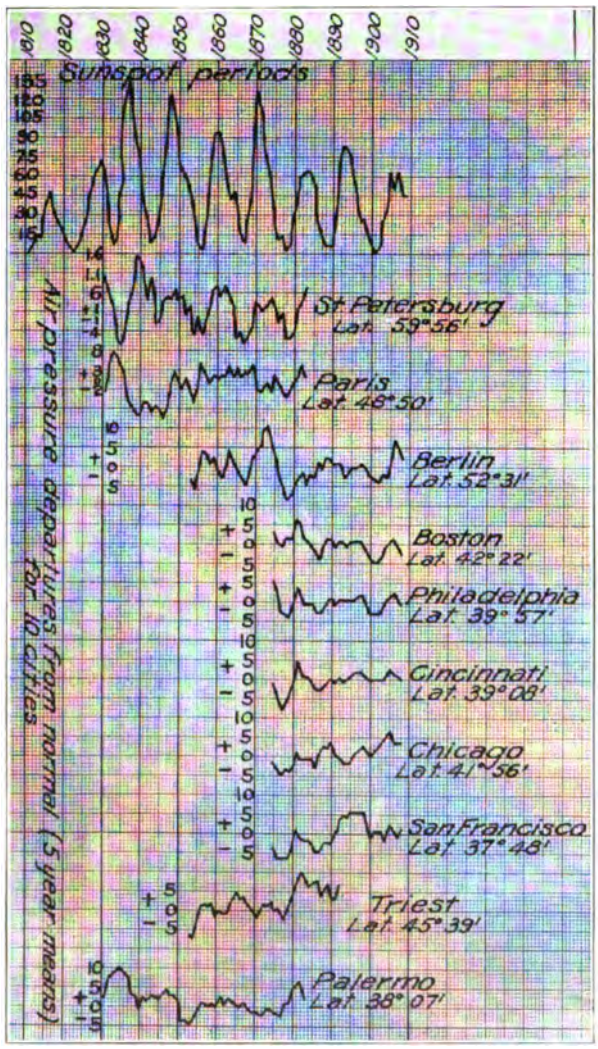


**Chart 2.—Air-pressure departures from normal in ten cities.**

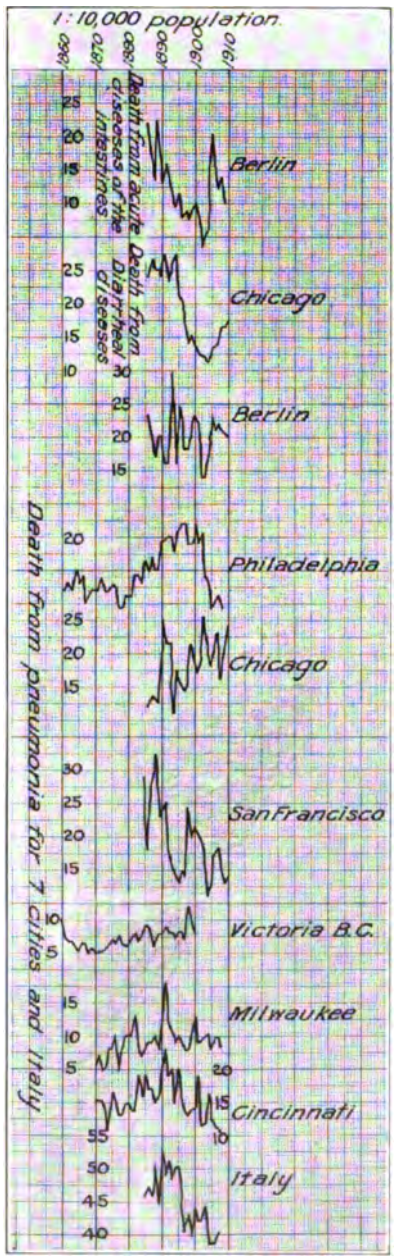


**Chart 3.—Deaths from pneumonia in seven cities and Italy.**

Chart 3 proves to a certainty the simultaneous appearance of enteritis and pneumonia epidemics on our hemisphere.

The mortality figures are of the ratio of 1:10,000 population. They represent acute diseases of the respiratory organs at Berlin, pneumonia (all forms) at Chicago, pneumonia "lobar and unqualified" for 1900 to 1908 at Philadelphia, Milwaukee and Cincinnati (U. S. Census Reports) and "pneumonia," according to E. F. Wells,[7] for the years before 1900 at those three cities and at Victoria, B. C., and they represent bronchitis and pneumonia (all forms) for the kingdom of Italy and San Francisco. Although the figures are not homogeneous, still by far the largest percentage of them refers to acute pneumonia. The enteritis figures represent enteritis (all forms) and since 1908 also convulsions at Chicago and acute diseases of the intestines at Berlin.

The figures for New York, as given by L. Emmett Holt,[8] and those for San Francisco practically agree with those of Berlin and Chicago. The time covered by my tables comprises fifty years for Philadelphia, forty for Victoria and twenty-five years or more for the other cities and Italy.

The enteritis lines are surprisingly uniform. Berlin and Chicago show practically the same synchronism in the rise and fall of this mortality. A period of about sixteen years intervenes between the last and the present high figure.

The pneumonia lines show the peculiarities of latitude and of the locality of the district where the epidemics occur. Some of them represent in a striking way the prevalence of relatively high or low pressure at such districts.

Cincinnati has the highest sea level pressure (763.6 for the year) on this chart and the highest pneumonia mortality, while Victoria, with a pressure of 762.0, has a lower mortality in proportion.

7. Wells, E. F.: THE JOURNAL A. M. A., Feb. 4, 1905, p. 361.
8. Holt, L. Emmett: THE JOURNAL A. M. A., Feb. 26, 1910, p. 682.

Milwaukee and Boston in a similar way have a lower mortality than Chicago and Philadelphia. The high mortality of the colored race from pneumonia in southern states gains a different aspect when we consider the high pressure area in which they live. In general, we find the lines of pneumonia mortality on the northern hemisphere to follow almost precisely the barometric gradients. This relation becomes qualified apparently by the solar activity existing during, or preceding, anticyclonic weather. For instance, we know from history, that from 1831 to 1835 there swept over our hemisphere a very great epidemic of grip and pneumonia—the greatest of that century before 1889—and we find then the highest air-pressure of that period registered at a time, when solar activity was lowest. The appearance of the 1889-90 epidemic was again heralded by abnormally high air-pressure and very low solar activity, while low air-pressure we find to be the rule during low solar activity.

Such exceptions seem to be determining factors and should be carefully considered in reference to the problem before us.

For the present, we simply record the very uniform increase of pneumonia mortality in cycles, that remind us at once of the three to four years or longer solar periods. The greater prevalence of enteritis seems to be linked to epochs of even longer periods.

I wish to call your attention now to some of the most recent work in reference to the question before us.

Physicists[9] have brought out the facts that the circulating atmosphere—the cloud zone—ends at about six miles height; oxygen, diminishing gradually in its percentage of the atmosphere, cannot be found at about forty-five miles height; nitrogen, increasing first to twenty-one miles, then diminishing rather rapidly, ends at about fifty miles height. Oxygen and nitrogen are then superseded by hydrogen. The amount of hydrogen and argon near the surface of earth is still a matter of controversy.

9. Wegener, A.: Beitr. z. Phys. d. Atmosph., June, 1910.

Two kinds of polar lights are seen in this atmosphere at a height of about thirty-six and about three hundred miles respectively. They represent the cathode rays, coming from the sun and deflected by the magnetic field of the earth. They appear in cycles which follow quite accurately those of the sunspots, both having their maxima often in the same year and their minima likewise. Only seldom a difference of one to three years is recorded. A certain dependence of air-pressure conditions on polar lights seems established in the vicinity of the latter.

Further investigation[10] proves that "the total amount of violet and ultra-violet in the solar radiation changes from time to time—a change in the relative intensity of the violet seems definitely established—and it seems quite probable that this intensity must be least at the time of maximum sunspot disturbance."

In regard to violet and ultra-violet radiation it seems important that "ozone is produced by the action of ultra-violet light on cold dry oxygen." "The amount of ozone in the outer atmosphere must, therefore, vary with the amount of ultra-violet radiation sent out by the sun." "When this ultra-violet solar radiation is at a minimum, presumably during a sunspot maximum, the amount of ozone in the upper layers of the atmosphere will be a minimum, unless maintained by some other process (auroral discharges).

"On the other hand, with a maximum of ultra-violet radiation, presumably during a sunspot minimum, there will be a maximum amount of ozone."

Humphreys furthermore claims that auroral displays which exist inside the oxygen level must be accompanied by production of ozone. He adds:

> The equator to pole circulation of the upper atmosphere and the paralleling of magnetic lines of force by auroral discharges might well lead to a greater amount of ozone in the

10. Humphreys, W. I.: Solar Disturbances and Terrestrial Temperatures, Astrophys. Jour., September, 1910.

**upper air of temperate and polar regions than in those of the tropics. . . .**

**The amount of ozone in the atmosphere, since it results from the action both of auroral discharges and ultra-violet radiation, that seem to increase and decrease oppositely, *though not necessarily equally*, tends to remain more or less fixed.**

But it is the exception to the rule that may bring disaster.

In conclusion, we may assume that since the periods of solar activity, of auroral discharges and of air-pressure conditions are so closely interwoven with one another and with ultra-violet radiation and the periodic appearance of the epidemics in question, that it is of the utmost importance to renew the critical analysis of the air during different air-pressure conditions and at different parts of our hemisphere.

Research should be directed, for instance, to the amount of water contained in the atmosphere surrounding us, to resulting electrical conditions and to the effect of such agencies and of solar radiation on the mucous membrane and the body.

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# A CLINICAL STUDY OF MOBILITY OF THE HEART

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It has long been known from bedside study, and more recently from the use of the *x*-rays, that the heart occupies no fixed position in the thorax. The heart is held suspended by its large vessels and is in intimate relation with the walls of the thorax, the mediastinal tissues, the lungs, and the diaphragm. It is evident that the position of the heart may, therefore, be modified by abnormalities of any of the supporting structures, as mediastinal tumors, pleural effusion, pulmonary disease, particularly deformities resulting from tuberculosis, and by abdominal conditions which modify the position of the diaphragm, such as enlargement of the liver, ascites, intra-abdominal growths, and pregnancy. The physiologic factors which modify the position of the heart are, (1) respiration and (2) changes in the position of the body. I have concerned myself only with the latter in this study. Other causes of cardiac displacement will be mentioned only incidentally.

Cherchevsky[1] first called attention to abnormal mobility of the heart. In forty cases studied to determine the effect of changes in position of the body on the apex-beat, he found the mobility to be normally from 1.5 to 3 cm. In nineteen cases it varied from 4 to 7.5 cm.; there was slight mobility in six cases and no movability

1. Cherchevsky: La mobilité du coeur et sa valeur diagnostique, Gaz. méd. de Paris, 1887, p. 629.

in fifteen. He considered a range of mobility exceeding 3 cm. as abnormal. In arteriosclerosis, mobility was greatly diminished or absent.

Rumpf[2] concluded from a similar study that the absolute as well as the relative heart-dulness is normally movable about 2 cm. to the left in the left lateral position, and 1.5 cm. to the right in the right lateral position. In many cases the apex-beat remained in the same place, but it often showed a displacement of 2 cm. in a change of posture. Rumpf described five cases, in which the mobility of the heart toward either side amounted to 4 cm., which he designated as "movable heart."

Pick[3] examined 1,000 healthy persons. The majority showed no perceptible difference in the position of the apex-beat and in the percussion sound in different postures of the body. There was slight lateral mobility to the left on assuming a left-sided position in 60 per cent. of the cases, and the apex-beat moved from 1.5 to 2 cm. He described seven cases of movable heart, in which the apex-beat was displaced 4 to 6 cm. to the left.

Hoffman[4] found that the various grades of mobility of the heart were easily recognized by means of *x*-rays, and concluded that marked movability is of considerable importance to the state of health.

Schmidt[5] concluded that movable heart is often associated with cardiac neurasthenia.

Leusser[6] described several cases of movable heart and considered a displacement of the apex-beat of 3 cm. or more, to the left in the left lateral position, as abnormal.

Rummo,[7] in addition to increased mobility of the heart, described a condition in which there was sagging of the heart from its normal position over the

2. Rumpf: Ueber Wanderherz, Verhand. d. 7 Cong. f. inn. Med., 1888, p. 221.
3. Pick, A.: Ueber das bewegliche Herz (cor mobile), Wien. klin. Wchnschr., 1889, p. 747.
4. Hoffman: Verhandl. d. 16 Cong. f. inn. Med., 1898, p. 216.
5. Schmidt: Deutsch. med. Wchnschr., 1901, No. 16, p. 242.
6. Leusser: Ueber Wanderherz, München. med. Wchnschr., 1902, No. 26, p. 1095.
7. Rummo: Sur la cardioptose, Deutsch. med. Wchnschr. Vereinbeilage, 1900, p. 228.

diaphragm, due to relaxation of its supports, and introduced the term to such cases as "cardioptosis." There was no necessary relationship between cardioptosis and enteroptosis. He found both a partial and a complete ptosis, where the heart rests entirely on the diaphragm.

Braun[8] maintains that cardioptosis should be differentiated from movable heart. He does not consider the latter a disease, nor does he think there is justification for attributing neurasthenic heart symptoms to increased mobility of the heart.

Einhorn[9] found cardioptosis in 2.4 per cent. of 926 cases, eighteen men and four women. In the cases of cardioptosis he found it associated with increased mobility of the heart in a number of cases. He regards nervous disturbance of the heart, palpitation, vertigo, and occasionally inability to lie on the left side, as due to cardioptosis. In his opinion, cardioptosis is a distinct clinical entity, equally with enteroptosis.

Hunter[10] described a case of paroxysmal tachycardia and arhythmia with an unduly movable heart. The movability of the heart amounted to 2 inches with change of position from one lateral posture to the other. He was unable to determine that change of posture influenced the paroxysms of tachycardia.

Elliott[11] recently studied the movability of the heart and aorta in health, as evidenced by radiographs taken in unusual positions. That the heart is fairly movable in health and that it may be forced into unusual positions by abnormal physical means is generally understood, but that it is as freely movable as it is, and that its mobility may be made to assist in the interpretation, or may lead to misinterpretation of radiographic findings, unless taken into consideration, has not been

8. Braun: Ueber das Wanderherz, Centralbl. f. inn. Med., 1902, No. 35, p. 873.
9. Einhorn: Cardioptosis and its Association with Floating Livers, Med. Rec., 1903, lxiii, No. 17, p. 647.
10. Hunter: Case of Paroxysmal Tachycardia and Arhythmia with Unduly Movable Heart, Glasgow Med. Jour., lxix, 367.
11. Elliott: Movability of the Heart and Aorta in Health as Evidenced by Radiograph Taken in Unusual Positions, Quart. Bull. Northwestern University Med. School, 1911, xii.

sufficiently recognized. A radiograph taken with the patient lying on the right side, respirations at rest, shows that the heart is largely moved to the right of the vertebral column. Similarly, with the patient lying on the left side, respirations at rest, the entire heart shadow is carried to the left, leaving the right border of the vertebral column free and unaffected by the heart-shadow. With the patient lying on the right side, the aorta casts a shadow which extends 4 cm. to the right of the vertebral column, whereas with the patient lying on the left side, the shadow cast by the aorta does not appear to the right of the vertebral edge at all.

Krehl[12] found that the position of the heart changes with that of the body and that the apex-beat is often found to be displaced to the left a few centimeters when the individual lies on the left side. In some cases, however, displacement was so great that the term "wandering heart" was justifiable. In the right lateral position, the apex-beat in healthy individuals either remains unaffected or is displaced only by very little to the right. The change from the horizontal to the vertical position, and vice versa, has no appreciable effect on the apex-beat. Krehl considers that extreme mobility of the heart is due to great loss of intrathoracic fat (starvation cures, tuberculosis) and that in these cases the cardiac displacement causes more or less distress when the patient lies on his side, possibly on account of contraction or kinking of the large vessels.

Determann[13] considered that in nervous persons abnormal mobility of the heart appears to be not uncommon and causes subjective cardiac symptoms. A comparison with movable kidney naturally suggested itself.

Hoffman[14] states that when the position of the diaphragm is high and the heart is abnormally movable

12. Krehl, L.: Diseases of the Myocardium, Nothnagel's Encyclopedia, Am. ed. W. B. Saunders & Company.
13. Determann: Ueber die Beweglichkeit des Herzens, Deutsch. med. Wchnschr., 1900, No. 15.
14. Hoffman, A.: Acute Herzdilatation und Cor mobile, Deutsch. med. Wchnschr., 1900, No. 19.

so that the larger portion of its area comes in contact with the chest-wall, dilatation may be simulated. He believes that many cases of so-called cardiac dilatation are in reality only examples of this condition. Error can be avoided by testing the mobility of this organ.

Dietlen[15] and Moritz[16] have made extensive orthodiagraphic studies of the size and position of the heart under normal and pathologic conditions. Conner,[17] recently summarizing some of their many interesting facts on this subject, states: 1. With a change from the recumbent to the erect position, there is a distinct sinking of the heart from 2 to 4 cm., corresponding to the lower position of the diaphragm and liver, and that with this the heart assumes a more nearly vertical position while the width of the shadow is considerably lessened. 2. In old age there is regularly a lower level of the diaphragm and a correspondingly lower position of the heart, but in this case the organ, instead of having a more vertical position than usually occupied, was more nearly transverse. The explanation of this is probably to be found in the relaxation of the attachments of the great vessels, by which the heart is held in position. 3. In women the position of the heart is on the average an intercostal space higher than in men. 4. In asthma and emphysema there is a marked sinking of the diaphragm and heart, and to this fact often, more than to the overlapping of the heart by the voluminous lungs, is to be ascribed the great diminution of the heart sounds in the second intercostal space and the low position of cardiac dulness.

The present contribution to this subject is the result of a study of 193 cases. Of this number, forty-nine were apparently healthy. The remaining 144 were private patients or routine cases studied in my wards at the Los Angeles County Hospital.

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15. Dietlen: Arch. f. klin. Med., No. 88, p. 55.
16. Moritz: Methoden der Herzuntersuchung, Deutsch. Klin., iv, pt. 2, No. 15.
17. Conner: The Clinical Study of Heart Cases, Am. Jour. Med. Sc., June, 1908, p. 790.

In studying the movability of the heart in different positions of the patient, the absolute or superficial cardiac dulness was used and determined by feeble percussion. In determining the change of the apex-beat in different postures, the usual point of maximum intensity of the apex-beat was ignored. That point of the heart coming in contact with the palpating finger farthest downward and to the left was considered the true apex.

The conclusions obtained were the result of a second examination, or were controlled by two examiners, so that a fair degree of accuracy may be assumed. In all cases in which there was doubt as to the exact position of the apex-beat or of the border of cardiac dulness, opinion was suspended and these do not enter into the ultimate findings.

One of the most striking facts observed was the discrepancy between the amount of displacement of the apex-beat and that of the cardiac dulness in the change of position of the patient. The change in the apex-beat amounted in some cases to 5 cm. or 6 cm., while that of the cardiac border of dulness was only 2 cm. or 3 cm., and vice versa, so that, as far as our experience teaches us, these two factors are not always as constant as one might expect them to be. This may be due to the fact that in changing the position of the body there occurs a twisting of the heart on its long axis, thus making considerable alteration in that portion of the heart which comes in contact with the chest-wall as the apex-beat.

In the 193 cases there were nine in which there was total displacement of the heart downward, the so-called cardioptosis of Rummo. In seven of these there were clinical signs of atheroma of the aorta. The low position of the apex in these cases on first impression suggested aortic valve disease until the cardioptosis was discovered, which to me emphasizes the importance of invariably testing the mobility and position of the heart

before assuming from an abnormal position of the apex-beat that dilatation or hypertrophy is present. Close examination in all of these cases of cardioptosis showed that the heart *en masse* was displaced downward from one to two interspaces.

Of the forty-nine persons in health, consisting largely of high school students, the average displacement of the apex-beat from the dorsal position to the left lateral position was 3.02 cm. to the left, while the right border of cardiac dulness changed only 1.04 cm. The greatest change in the apex-beat was 5 cm. and that of cardiac dulness 8 cm.

The smallest change in the position of the apex-beat was 2 cm. and that of cardiac dulness was in patient M. K., aged 15, apparently well, in whom there was no change in the movability of the heart from the dorsal to the left lateral.

Of the 144 patients selected routinely, suffering from various diseases, the average change in the apex-beat with the patient changing from the right lateral to the left lateral position, was 3.9 cm., the change in cardiac dulness, 2.7 cm. The maximum displacement of the apex-beat was 14 cm. in a case of pulmonary tuberculosis. In another tuberculous subject the displacement amounted to 10.5 cm.; in another, 13.5 cm. In one case of mitral regurgitation the displacement of the apex amounted to 9 cm., in another to 7.5 cm., and in still another to 8.5 cm. In other patients with the same diagnosis, however, the mobility of the apex was normal or diminished, so that the movability of the heart in these conditions was by no means characteristic. The greatest mobility of the cardiac dulness was 12.8 cm., in a case of pulmonary tuberculosis. In a second case of tuberculosis it was 12 cm. In the cases of cardiac lesions, twenty-five in number, excluding six cases of pericarditis with adhesions, the displacement of the apex-beat was 3.6 cm., and the change in the cardiac dulness with change in position of the patient from the

right lateral to the left lateral was 3.3 cm. No differences in the displacement of the heart were observed in mitral and in aortic valvular lesions. In the six cases clinically diagnosed as pericarditis, two being confirmed at autopsy, with adhesion of the outer pericardium to surrounding structures, there was fixation of the heart; no change in either the position of the apex-beat or cardiac dulness occurred when the patient changed from the right to the left lateral postures.

The impressions from this study, imperfect as it is, are, first, that the determination of the movability of the heart is of considerable value in the differential diagnosis of cardiac dilatation, and that before assuming that the heart is dilated to the right or to the left, the movability of the heart should always be determined.

Secondly, the immobility or fixation of the heart should always arouse the suspicion of adhesion of the pericardium to neighboring organs. There is probably no serious heart lesion diagnosticated less frequently, clinically, than pericarditis with adhesions. Since systolic retraction of the interspaces and other signs of this condition are so frequently absent, it seems that it would be well to emphasize immobility or fixation of the heart as one of the signs of pericardial adhesions.

My thanks are due Drs. J. W. Nevius and J. W. Bardill for assistance in the production of this paper.

In addition to the authorities already cited, the following may be consulted:

Pottenger: Displacements of the Heart and Diaphragm, Interst. Med. Jour., June, 1911, p. 605.

Groedel: Roentgen Rays in Heart Diagnosis, Interst. Med. Jour., June, 1911, p. 615.

Satterthwaite: Mobility and Malpositions of the Heart, Internat. Clin., ii, ser. 21, p. 55.

# VERRUCA PERUANA OR CARRION'S DISEASE

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## HISTORY AND DISTRIBUTION

Verruca peruana, or Carrion's disease, is an infectious disease endemic in certain districts in Peru. It is characterized by fever, rheumatoid pains, anemia and an eruption which develops into bleeding, warty tumors. Verrugas, to use the Spanish term, caused many deaths among the ancient Peruvians and among the followers of Pizarro during the conquest of Peru.

Various writers of that country, since 1730, have described the disease, but it was brought into greatest prominence in 1870 during the construction of the Oroya Railroad over the Andes mountains. Many of the foreign laborers were attacked by a strange and fatal disease which was given the name of Oroya fever and the connection of this fever with the external eruption, previously known as "verrugas," was established during this period. Their unity was illustrated by the case of Wilson, a mining engineer, who after an attack of Oroya fever returned to the United States and afterward developed a typical case of verrugas.

Carrion, a Peruvian medical student, inoculated himself, Aug. 27, 1885, on each arm with blood from a tumor of a case of verrugas; initial symptoms appeared September 17 and his death occurred October 5, the thirty-ninth day after inoculation, having passed through all the stages of Oroya fever. This experiment established still more fully the relation of Oroya fever and verruca and showed the infectious nature of the disease.

While verruca was formerly endemic in several countries of South America, it is now limited to Peru, being found in three departments, Ancachs, Libertad and Lima; and the infected areas are confined to certain deep river valleys of high altitude. Any person is liable to infection, regardless of age or sex, although organic debility seems to be a predisposing cause. Natives of the infected districts are immune, but all others are liable to contract the disease, even when merely passing through the country. Intra-uterine infection occurs, children being born with the disease.

The lower animals are liable to infection and present the same symptoms as human beings, but the external lesions grow much larger.

No authentic case of infection by personal contact has been known to occur outside of infected districts. Verruca, in common with many other diseases, has been confused with malaria, to which the character of the fever bears a close resemblance. In many ways it closely resembles yaws, but there are so many distinctive points of difference that it hardly seems probable that it is a form of that disease, as is claimed by some authorities.

### BACTERIOLOGY AND PATHOLOGY

But little animal experimentation has been done, consequently the etiology has not been shown conclusively and the method of transmission is unknown, but it is very probable that it is conveyed by some form of insect life. An organism, apparently a bacillus, is found in the red blood-cells during the febrile period and in the tissues of the local lesions. It presents two forms, found in different stages of the disease, one closely resembling, morphologically, the tubercle bacillus, the other much thicker and apparently an involution form. This organism is 2 to 6 microns in length, has rounded ends, is motile, contains two or three granules resembling spores and is gram-negative, but stains well with methylene-blue. It grows readily on bouillon at a temperature of

98.6 F., cloudiness appearing on the second day. The organism from this culture is from 10 to 12 microns in length, and stains well with gram and carbol-fuchsin. Much careful investigation will be necessary to prove definitely whether this organism is really the specific cause of verruca as it now appears to be.

On autopsy, all organs are found pale and bloodless, the liver and spleen are frequently enlarged and there is constant enlargement of the lymphatic glands—a diagnostic point. There is hyperplasia of Peyer's patches and congestion of the intestinal mucous membrane.

### SYMPTOMS

The period of incubation is not sharply defined; in Carrion's case transmitted by inoculation, it was twenty-one days, but if contracted in the natural way it may be from fifteen to forty days. The invasion is slow, beginning with headache, pains in the lower extremities, chills followed by fever, thirst, anorexia and insomnia. The digestive system presents the symptoms of an acute fever, the liver, spleen and lymphatics are engorged and petechia frequently appear.

The fever follows a remittent or intermittent type and during the fastigium varies from 100 F. in the morning to 104 F. or higher in the evening, extending over a period of twenty-five or thirty days.

Anemia is the predominating symptom, coming on very rapidly and much resembles that following hemorrhage. The red blood-cells are reduced to 1,000,000 or 500,000 and there is marked leukocytosis with a great increase of polynuclears.

The skin is white and wax-like, the lips, tongue, gums and nostrils blanched and the nails discolored. Icterus is visible in the conjunctiva, the respiration is rapid, often with dyspnea, the pulse from 120 to 140 and systolic murmurs are heard at the base of the heart extending into the vessels of the neck, the latter symptom being very annoying to the patient. Epistaxis is frequent and

serious, but hemorrhage from the bowels occurs less often. Edema is often present in the lower extremities, rarely becoming general.

Vertigo is so severe that the patient cannot sit up for fear of syncope. Mild delirium occurs in the evening and hiccough is frequent.

Many patients succumb within twenty-five or thirty days, but if the patient survives the febrile period the symptoms gradually decline until the appearance of the eruption, when they recur. In most instances the eruption is not noticed until after the decline of the fever, but in some cases it appears simultaneously, although in the former instance it is quite possible that the eruption escapes notice, or may be located internally.

It was formerly thought that Oroya fever was a distinct stage of verruca, but later studies show that no sharp line can be drawn between the fever and the eruption and the division is made only for convenience of study.

In some cases there is a sudden onset of high fever, all other symptoms are very severe, and death occurs in a few days showing the eruption on the skin, small, discrete and with no tendency to multiply, or the disease may prove fatal without the appearance of the external eruption.

In a majority of cases there is an intermediate period of from forty days to four or five months before the eruption is seen. When it does appear, the digestive and nervous symptoms are increased in severity, and the anemia is more marked, being identical with that of the initial fever, but it develops more slowly. The fever of the eruption also follows a remittent or intermittent type, rising to 104 F. or higher and varies with the amount and form of the eruption. Edema is more constant than during the early stages, it is often limited to the lower extremities and is due to the induration caused by the eruption with the consequent compression of the venous circulation. The muscular and articular pains recur, the joints being tender and often tumefied.

There are two distinct forms of the eruption, miliary and globular, often difficult to classify, as there are all grades between the two extremes. The miliary form, the smaller, occurs both externally and in the deeper tissues.

Externally, this form is located above the true skin and may originate in three ways: a petechia beneath the Malpighian layer, as a sort of rosy drop more or less transparent, or as a slight elevation of a dead white tint resembling hypertrophied papilla. In whatever manner it first appears it grows gradually and develops into an elevated papule, dark, glossy and slightly pointed. In this form the papule varies in size from the head of a pin to that of a small pea, the smaller ones sessile, the larger tending to pediculate.

Exfoliation and bleeding occur, the larger ones ulcerating and discharging a yellowish liquid which forms a crust. A retrograde process follows and the growth disappears, leaving a slight stained appearance of the skin, which is transient.

The miliary eruption may be localized or general, discrete or confluent, and is located especially on the extremities and about the face, the palms, soles and body being usually exempt.

They occur on the mucous surfaces in all parts of the body, on the peritoneum, in the liver, spleen, kidneys, lungs, pancreas, testicles, periosteum, bones and brain. Those on the conjunctiva form small, flat button-like elevations the size of a millet-seed; in the nose they are larger and are the cause of the epistaxis. The brain lesions are the size of a pin-head, and located at the base, in the chorioid plexus and on the arachnoid membrane. It is a notable fact that the eruption always begins in the connective tissues and never in the parenchyma.

The globular form is found only externally and consists at first of a small subcutaneous elevation, tender and resistant to the touch, and like the miliary has a predilection for the extremities, the face and especially the ears. As the tumor grows, the overlying skin

becomes purple, painful on pressure and in appearance and consistency resembles a furuncle. It finally becomes conical, the skin grows thinner and is pierced by the growth, which now assumes a globular form and shows a tendency to pediculate. Fissures form and ulceration with hemorrhage are subsequent symptoms. This form varies from the size of a hazelnut to that of an orange.

In those of medium size, subinvolution begins, the growth becomes pale and shriveled, falls off and cicatrization takes place; but when they are large, gangrene, secondary infection and extensive suppuration are common.

Both forms may be found in the same case, or they may alternate, the period of eruption being from six months to two years. In the section, a verruca tumor somewhat resembles a sarcoma, having a stroma similar to embryonic tissue, and a circumscribed adherent wall. It is highly vascular, the blood-vessels having the appearance of sinuses.

Pneumonia, enteritis and paratyphoid are common complications, and secondary infection of the eruptive lesions may result in septicemia.

### DIAGNOSIS AND PROGNOSIS

The diagnosis is not always easy, but in a person who gives a history of having been in the infected districts, showing the symptoms of fever, anemia, vertigo, rheumatoid pains and enlargement of the lymphatic glands, verruca should be strongly suspected. When the eruption appears it is easily recognized.

The enlarged liver and spleen are not so constant as in malaria; in the latter the anemia comes on more slowly, prostration is not so severe, lymphatic enlargement is absent, the action of quinin is positive and the plasmodium is found in the blood.

Yaws, apparently a very similar disease, is not congenital; the yaws appear on the body as well as on the extremities, the general health is little affected, there

are no visceral changes, the mortality is low, and the *Treponema pertenue* is found in the eruptive lesions.

The prognosis is grave, the mortality, according to some authorities, being as high as 90 per cent. Most of the deaths occur prior to the appearance of the eruption, and when it appears the outlook is more favorable, especially if it comes out rapidly and becomes general, but when it is partial or pale and atrophies without the general condition improving, it is not so good.

### PROPHYLAXIS AND TREATMENT

Until the manner of infection is known, the only prophylactic measure to be recommended is to remain outside the districts known to be infected.

It is not considered necessary to isolate the patient, as there is no danger from personal contact. The patients whom I have seen were being cared for in the medical wards of Dos de Mayo Hospital, Lima, where they are received and treated without fear of infection.

The therapeutic resources are limited and consist principally of symptomatic and supportive treatment. Quinin is indicated if malaria exists as a complication, but it has no effect on verruca itself. The digestive system should be put at rest, the food being light and digestible, and when vomiting is constant, rectal feeding is necessary. Tonics and reconstructives are very useful when they can be borne. Saline solution by rectum and intravenously is used to great advantage during the critical part of the febrile period.

In presenting this paper, I do not wish to be taken as an authority on verruca, but merely give the impressions gained by a rather limited study of the disease while on a recent visit to Peru, together with information gleaned from literature which it is believed is but little known to the profession of the United States.

Verruca has not been widely investigated as yet, and it is believed that a further study of this interesting disease will prove it to be insect-borne and perhaps throw

some light on other diseases, the etiology and transmission of which are not yet understood.

It is desired to render proper credit to Dr. Ernesto Odriozola of Lima, Peru, whose excellent monograph on verruca has been freely consulted in the preparation of this paper, and to extend thanks to Dr. Julian Arce, Director of Health of Peru, for presenting me with a copy of this work. Finally, I would acknowledge my obligation to my wife for the translation from the French of the above monograph.

# THE TREATMENT OF INTESTINAL AMEBIASIS

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As is the case in so many other infections, especially those manifesting themselves as more or less chronic processes, the natural tendency in amebic infections of the colon is toward recovery.

In routine post-mortem examinations in Manila, all stages of healing and even healed amebic ulcers are very frequently encountered where amebic disease had not been suspected during life, and where no dysenteric therapeutics had been employed. Furthermore, we have a large number of records of cases of undoubted amebic ulceration of the colon, characterized by an unmistakable clinical picture with amebas in the stools and in some cases the diagnosis confirmed by sigmoidoscopic examination, in which apparent recovery took place without any special or sufficient treatment and in which post-mortem examination from one to five years later failed to show any ulceration, visible scarring or other abnormality of the colon.

We conclude from these facts that there is not only a natural tendency to recovery from the disease, but that such recovery actually takes place in a considerable percentage of patients and that recovery in many instances may be so complete as to leave little or no permanent scarring of the intestinal wall.

Another factor which may increase the difficulty of accurately determining the results of treatment goes back to the pathology of the infection. Formerly, our conception of the pathology of the amebic lesion con-

sisted mainly in a definite and typical type of ulceration. Later studies have shown that the types of ulcers vary considerably and several decidedly different lesions have been described. Wooley and Musgrave, and Rogers not only have described and illustrated erosions too insignificant to be called ulcers, but the former authors have noted epithelial cell-death around nests of amebas situated in the follicles of the intestinal mucosa, without loss of continuity of tissue—the preulcerative lesion. At the time of the publication of these results, all these lesser processes were considered but early manifestations of the more extensive and typical destruction of tissue.

For a number of years, my opinion has been growing stronger that all expressions of amebic harm are not to be found in ulceration of the mucosa, and that there is a definite amebic pathology in which there is no break in the continuity of the mucous membrane of the bowel.

This proposition is not susceptible of proof at the present time, but there are many data which may be used in support of such a hypothesis, and if we accept the theory of amebic pathogenesis at all, I do not see any other explanation of some of the clinical types and pathologic conditions so commonly encountered in zones where amebic infections are frequent.

There does not appear, *a priori,* any more reason to assume that ulceration of the colon is a *necessary* and constant lesion of amebic infection than that ulceration of the follicles of the ileum is necessarily a result of typhoid fever. In many cases of amebic ulceration of the colon, a catarrhal condition of parts of the intact mucosa may be found, in which sections show a suggestive relationship between the areas of degenerating epithelial cells and the location of colonies of amebas. The acceptance of amebic etiology of this condition is hypothetic, but personally I believe that future and more accurate studies of the pathology of this infection will recognize an amebic colitis without ulceration of the mucous membrane.

THE IPECAC TREATMENT

One may obtain from the literature of the subject pretty good authority for the most divergent views as to the value of ipecac in dysentery. It is not my intention to review this mass of literature which consists largely in conclusions arrived at as a result of that very difficult and often fallacious test, "clinical results."

If we assume, as we must, the honesty and accuracy of the observations of many experienced workers who have reached diometrically opposite conclusions from their experiences with this drug, it is reasonable to conclude that there are unknown or overlooked factors which have influenced their conclusions.

The three most important of these factors are:

1. The incomplete knowledge of the pharmacology of ipecac.
2. The different conceptions of "dysentery."
3. The various definitions as to what constitutes a cure in "dysentery."

Very little is known of the physiologic action and other pharmacologic properties of ipecac, and because of this deficient knowledge it is impossible for manufacturing chemists to standardize their products, with the result that there may be a considerable variation in the efficiency of the drug as it is found on the market. Many authorities consider this probable variation in the different preparations of the drug as responsible, at least in part, for the divergent therapeutic results obtained from its administration in dysentery. Such a position seems well taken, for there is every reason to believe that the unknown active principle of this drug may vary in strength as much as that of any of the other well-known medicinal plants; and until pharmacologic standardization of ipecac becomes possible, probable variation in the strength of the drug must be taken into consideration in drawing conclusions as to its therapeutic value.

The drug very probably exerts some very decided action on the intestine as is proved by the results of its administration to healthy persons:

Ten healthy persons with no symptoms of gastro-intestinal disturbance were given 3-gram doses of powdered ipecac in salol-coated pills in a manner similar to that employed in the "ipecac treatment" of dysentery.

Seven of these persons developed diarrhea, which in four was severe with frequent stools and the condition lasted from two to four days; in three there was considerable abdominal pain and slight tenesmus. Special preparation to prevent nausea and vomiting usually are not necessary with Filipino patients because, in the majority of instances, the administration of the drug in ordinary gelatin capsules is not followed by either nausea or vomiting.

Without doubt the most important factor influencing the various opinions regarding the value of ipecac in dysentery is the wide difference in the definition of "dysentery" among medical men. This statement is true to such an extent that if we carefully examine the literature with this point in view, it is possible to see a good deal of harmony in the results of actual experiments. In general, it may be stated that the majority of pro-ipecac literature deals with results obtained in acute and chronic "clinical dysentery" characterized by frequent stools with blood and mucus and usually accompanied by tenesmus. Whereas most of the writers who have made less satisfactory reports as to the value of the drug in amebiasis have considered the disease more from etiologic and pathologic standpoints and have thereby included many of these numerous cases of ulceration of the colon without "clinical dysentery" symptoms; cases which are rarely classed as dysentery—amebic or otherwise—in the reports most favorable to the ipecac treatment of the disease.

With a few notable exceptions, articles discussing the ipecac treatment of dysentery follow the above idea so closely that one may anticipate the author's conclusions by reading abstracts of his clinical case records. Such an analysis of the literature permits one general con-

clusion—which so far as I know never has been seriously disputed—that ipecac is a valuable drug in "clinical dysentery" of whatever etiology.

After a personal experience with the ipecac treatment in several hundred cases, it has seemed to me possible to estimate its value only in terms of "clinical symptoms," which we now know do not necessarily express the actual conditions existing in the colon in amebiasis.

In "clinical dysentery," as defined above, of whatever etiology, ipecac given in large doses, as usually recommended, is a valuable drug. In the majority of instances its administration is followed by a rapid subsidence of the symptoms and quick convalescence. In a smaller percentage of such cases it apparently does no good whatever, and in a not insignificant number its administration is followed by an aggravation of the symptoms which in some grave cases may at least hasten an unfavorable termination, particularly if, as may happen even with the greatest care, severe nausea and vomiting results from the treatment.

However, it must be remembered that it is in the class of "clinical dysenteries" that the best results are obtained with other forms of treatment beside that of ipecac. The natural course of an acute attack of dysentery is usually short and terminates in death or recovery. In a small percentage of cases "chronic dysentery" follows an initial acute dysentery, but in the majority of instances the chronic disease, particularly of amebic etiology, develops gradually and no such acute onset occurs.

Acute outbreaks, due either to an exacerbation or to intercurrent infection, are frequent in chronic dysenteries, particularly in amebic cases, and, if the patient can withstand the effects of the acute inflammation, a beneficial influence on the chronic process usually results. This is true particularly in intestinal amebiasis as is indicated by the following brief report of fourteen such cases.

In fourteen private patients suffering from intestinal amebiasis a cure with permanent disappearance of amebas from the stools has followed recovery from an intercurrent acute dysentery which in the four cases, in which the cause was studied, was due to the *Bacillus dysenteriæ*.

My attention was first directed to this point some years ago in the following case:

Mrs. C., an American, four years in the Philippine Islands, developed a typical attack of amebiasis with moderately severe clinical symptoms and with amebas in the stools. The diarrhea was intermittent and occasionally small amounts of blood were found in the stools. She was placed under treatment and the clinical symptoms subsided in about five days, but amebas were still present and continued so in many examinations during the next year. During this time there were several recurrences of clinical symptoms of the infection, and the patient lost about 10 kilos in weight. She refused to take treatment except during the time when she had diarrhea. More than one year from the time of the diagnosis of the amebic infection, the patient suddenly developed a typical attack of clinical severe acute dysentery. Amebas were present in the stools, and *B. dysenteriæ* were isolated by culture. The attack was a particularly severe one with the several symptoms of this condition, such as fever, frequent bloody mucous stools, tenesmus and prostration. During three days the patient was delirious, and stools were voided involuntarily. On the fifth day of the acute disease, there was a few motile amebas present and many cells of doubtful diagnosis. On the fifteenth day no amebas were found in the stools and none have been found since in many examinations. Convalescence from the acute dysentery was satisfactory, there has been no subsequent bowel trouble, the patient has regained her former weight, and is apparently perfectly well.

The other thirteen cases mentioned were somewhat similar to this, differing principally in the duration and severity of both the acute dysentery and the amebiasis and in the time of the disappearance of the amebas.

In two of the patients, amebas were found for one month after the acute attack and in one case for three months, but they finally disappeared without any special treatment of the disease.

I do not know how general such a condition as described in these cases of double infection may be, but the curative influence of the acute disease on the more chronic one of the amebic infection seems a decidedly positive one. This conclusion also is borne out by autopsy studies. I have several records and specimens of cases of old chronic amebic infection in which death occurred as the result of an intercurrent acute bacterial dysentery. At autopsy in these cases the pathologic picture is that of an acute inflammatory condition engrafted on the older amebic ulceration. The edges and bases and tissues surrounding the usual typical amebic lesions show decided changes. The dull, necrotic, undermined, chronic process has been changed to an acute one with congestion and hyperemia. The contents of the ulcers have changed from the indefinite, granular, foul-smelling material and mucus usually seen to the serous, mucoid material seen covering the surfaces in acute ulceration. Sections examined microscopically show a change from the necrotic, progressively destructive process of granular material containing amebas and with a small amount of cellular infiltration and tissue reconstruction surrounded by a practically non-inflammatory zone, to a typical acute process with hyperemia, edema, hemorrhages, and leukocytic infiltration.

### GENERAL MEASURES

The general management of cases of amebiasis is determined largely by the clinical conditions of the patient. "Clinical dysentery" with bloody mucous stools, tenesmus and the other usual symptoms, of whatever etiology, demands during such period absolute rest in bed, a very restricted milk-free diet and measures for the control of intestinal peristalsis and for the relief of pain. When the acute symptoms have subsided and in all other cases where the symptoms are less severe a much more liberal policy is indicated. Cases characterized by diarrhea, constant or intermittent, with more or less emacia-

tion and general debility with or without an occasional acute exacerbation with more severe symptoms form the large majority of those seen in Manila and constitute what may be called average cases, very chronic in character and usually lasting for years unless properly handled. In former publications I have recommended a liberal diet and some form of occupation requiring both physical and mental activity of a moderate degree in this class of patients, and such a recommendation is reiterated at this time. Such treatment being contraindicated only during acute outbreaks and in the presence of symptoms indicating interference with the digestion and assimilation of food. *Proper support of nutrition* is considered the first requisite in the treatment of this usually chronic affection, and there is no satisfactory evidence that a sufficient amount of properly prepared digestible food aggravates the disease or interferes in any way with the success of the treatment unless the "ipecac treatment" is being used, when a temporary restriction of the diet is essential.

Only such medication is indicated as that which perhaps may have a tendency to improve the patient's general condition, and in certain instances to meet special conditions, as excessive fermentation, hyperchlorhydria and other manifestations requiring special consideration.

LOCAL TREATMENT

Local treatment by bowel irrigation, either alone or combined with some other form of medication, gives the most satisfactory results in the majority of cases of amebiasis. To secure the maximum of efficiency this form of therapeutics requires special attention to certain details, particularly to

A. The manner and time of giving the enema.

B. The solution to be used.

In former publications I have recommended the use of the long rectal tube to be employed with the patient in the left lateral (Sims) position. The experimental

work of a number of investigators has proved the futility of trying to pass a long rectal tube through the sigmoid colon, and the same line of experiments, of showing the course of rectal tubes and fluids introduced by them by radiographic work with bismuth emulsions, has shown conclusively that no such special effort is required in order to get enemas to reach all parts of the large bowel from rectum to cecum. Indeed, it has been shown that the entire large bowel is easy of access by any form of enema provided sufficient quantity of fluid is used. In view of these results, the long 1- and 2-meter rectal tubes, formerly recommended and generally used in Manila, have been practically abandoned for the ordinary large-sized male rubber catheter which may be attached to an ordinary 2- or 3-liter irrigator, preferably made of glass.

In order to secure the best results from any form of rectal medication, the bowel must be distended by the substances employed. This object may be accomplished by using large amounts of fluid, and the result is materially influenced by the position of the patient and to a less extent by the condition of the lumen of the bowel at the time of the treatment.

The bowel capacity varies greatly in different individuals, due both to variation in actual size of the organ and particularly to its resistance to the introduction of foreign substances. Ordinarily, with proper care, from 2 to 3 liters of fluid may be used, but in many instances, particularly in women, as much as 4 liters may be introduced without any special discomfort to the patient. In those cases in which less than 2 liters of fluid can be taken, the condition may be assumed to be due to contractions of the bowel-wall, and if the best results are to be obtained from the treatment special preparatory treatment looking to an amelioration of the influence must be employed. Such treatment consists in a preliminary washing of the bowel, the use of sedatives, as opium in some form or, what is simpler and frequently sufficient

where there are no special contra-indications, the administration of 25 to 50 c.c. of brandy by mouth, ten or fifteen minutes before giving the enema. Alcohol is much less objectionable for this purpose than is opium, because of the repetition which may be necessary with each treatment until a tolerance for the enema is established as is sure to occur under favorable conditions. Since the appearance of Meltzer's and Shakler's work on the physiologic action of magnesium sulphate on peristalsis, this substance has been employed for the above purpose in 15 and 20 doses given four to six hours before the enema, with very encouraging results. The knee-chest position undoubtedly is the best one for any form of medicated enema. The physiologic reasons for this statement are obvious, and experience has shown that in the great majority of cases a larger quantity of fluid may be taken in this manner than in the Sims position and that it is retained with greater comfort to the patient. The only objections to the method are esthetic ones, and as patients, particularly women patients, rarely require assistance in taking such enemas after a single instruction, this objection becomes of minor importance. The bath-room floor with the patient stripped and a bath towel under knees and chest is a most satisfactory place for this treatment because of the privacy and convenience to both toilet and water; this method is one now largely practiced in Manila.

Enemas should not be given during digestion because the reversed peristalsis usually set up by such treatment interferes with the process of digestion and may aggravate stomach symptoms already present in this disease.

A very good time to take the treatment is just before retiring at night and the first thing after waking in the morning. One enema each twenty-four hours usually will be found sufficient, but in many instances two a day will give quicker and more satisfactory results. More than two treatments of this character in twenty-four hours never is indicated.

SOLUTIONS

A large variety of chemicals selected largely because of their supposed amebacidal properties have been used in the local treatment of amebiasis. As a matter of fact, very few of them are endowed with appreciable amebacidal properties and it is an open question, which will be discussed presently, whether or not whatever virtue the most successful ones may have is due to their amebacidal properties.

Of the list of such substances, thymol, quinin and silver nitrate are the three which have been proved to be of greatest value.

Thymol is by far the most efficient of the known amebacidal agents and it has been my main reliance in the treatment of amebiasis since its antiparasitic properties were so thoroughly demonstrated by J. B. Thomas.[1] On account of the difficulty in getting the drug in solution in water, the following formula has been worked out and has proved to be very convenient. and satisfactory:

| ℞ | Gm. or c.c. |
|---|---|
| Thymol | 25 |
| Alcohol | q. s. |
| Glycerin | 250 |

M. et Sig.—Add 10 c.c. to each liter of water used in enema.

This gives a finished product of approximately 1 to 2,000 solution of the drug which, when the additional dilution formed by the bowel contents is considered, brings the actual intra-intestinal solution well within the antiprotozoal limits of the drug which is very actively amebacidal in 1 to 10,000 solution.

There does not appear to be any particular choice between the various quinin salts. The bisulphate is freely soluble and well adapted for use. The drug may be used in 1 to 1,000 to 1 to 500 aqueous solution depending on the irritability of the bowel. One of the

1. Thomas, J. B.: Bull. Bur. Gov. Lab., Manila, 1904.

principal objections to quinin is the constitutional effects often produced by its absorption from the bowel, particularly in patients who are able to retain enemas for considerable lengths of time.

Nitrate of silver frequently proves of decided benefit in solutions of from 1/10 to 1 per cent. solution in distilled water.

The method of action of these and various other substances frequently used in colonic lavage is not understood. Formerly the amebacidal properties were considered the most important, but careful consideration of the morbid anatomy of the disease makes this hypothesis a very doubtful one.

The parasites which are intimately associated with the lesions, and which therefore may be considered the most dangerous ones, are so buried in the tissues that there seems little likelihood of their contact with the solutions injected. These lesions are constantly discharging millions of amebas into the lumen of the bowel, and amebacidal substances may destroy these and prevent their forming new lesions. It seems rational, however, to consider the intestinal reaction due to irritation of the bowel by the solutions as being probably more important than any direct antiparasitic property of the chemicals.

The effect of acute inflammatory condition of the bowel on the chronic amebic process has been indicated above, and it is probable that much of the good of the local treatment, of whatever character, is in its irritating influence and consequent altered blood-supply on the mucosa of the colon. Practically all the substances of proved value in local treatment are irritants, and it is a generally recognized therapeutic fact that the prognosis of the disease is more favorable in irritable bowels than in the kind in which the enemas cause little or no pain or discomfort to the patient. Tuttle's ice-water injection often gives excellent results in the disease, but is seldom used because of the intense pain frequently produced by the severe reaction in the intestinal wall.

### MISCELLANEOUS SPECIAL TREATMENT

As is to be expected from the chronic nature and the lack of a definite specific cure for the disease, numerous so-called specifics and especially efficient methods of treatment have been proposed from time to time. Of these may be mentioned, the saline treatment, the simaruba treatment, the bismuth treatment, tannic acid preparations of various kinds, calomel, metallic mercury, various crude tropical plants and several patent medicines which have secured considerable indorsement.

Some of the well-known chemicals of this list are of value in special conditions, but probably none of them are in any sense specifics, and all the rest of the remedies are useless or dangerous in the treatment of the disease.

The effect of mercury salts in the treatment of amebiasis deserves further investigation. During the last year I have had most encouraging results from the use of the protoiodid of mercury in old sluggish diarrheal types of the disease which reacted slowly to other methods of treatment.

The drug was administered just as it would be in syphilis, tablets of 0.015 gm. each were given from two to four times a day, the quantity being determined by the tolerance of the patient, the symptoms of intestinal irritation being controlled by small doses of paregoric when necessary and the drug pushed to the point of tolerance as determined by the mouth symptoms. This treatment should be continued for one to three or more months with occasional intermissions of a few days.

Of the sixteen patients whose records are complete and satisfactory, twelve were permanently free of amebas in from twenty to ninety days, and eight of these patients whose after-histories are known to me have remained free from amebas and from clinical symptoms from three to eight months after cessation of treatment.

### SURGICAL TREATMENT

Appendicostomy and cecostomy followed by colonic irrigation from above downward has been recommended

by a number of surgeons, particularly in cases of amebiasis which fail to recover under other methods of treatment. Our experience in Manila with this form of treatment is very limited. Dr. McDill has performed appendicostomy for this purpose on several patients, but the results hardly have warranted a continuation of the procedure. With improved methods of medical treatment and the removal of the old opinion that rectal irrigations do not reach the cecum, the conditions usually recommended before surgical interference is attempted are very rarely seen in our work.

COMMENTS

Whatever the form of treatment used in amebiasis, the old adage to "treat the patient rather than the disease" applies with particular force. Amebaphobia and overtreatment are two important factors in preventing recovery. Amebaphobia may not be confined to patients, but too often it influences the judgment and actions of the physician in a way very unfavorable to the patient's best interest.

Overtreatment is a very common error and comes from the desire to destroy all the amebas, which is practiced without due regard to the patient's general condition and is no more consistent with good therapeutics than it would be to employ remedies in typhoid or pneumonia, looking primarily to the destruction of the microorganisms causing these diseases.

It probably would be dangerous to consider any patient cured so long as amebas are discharged with the bowel contents, but with the patient in a satisfactory clinical condition this contingency should cause no particular alarm, because the accidents and complications of the disease are extremely rare in patients who have undergone a thorough preliminary treatment and whose clinical condition is kept in a satisfactory state by subsequent intermittent treatment.

As to choice of the methods of treatment, each case must be a law unto itself. The irrigation treatment is

the main reliance, particularly in what may be termed average or usual cases. Ipecac is particularly valuable in the presence of clinical dysentery and may be tried either alone or in combination with bowel irrigation. The substance used in enemas should be arbitrarily changed from time to time in cases where satisfactory progress is not being made by any one method of treatment.

With proper care, the prognosis of this disease is good as to recovery and, while the treatment usually requires several months, patients in the majority of cases may continue their regular vocations during treatment with an occasional rest and diet for a few days during exacerbations manifesting themselves as clinical dysentery.

In emaciated patients with old chronic cases of long standing, who have had no treatment, and in cases complicated by mixed infections and otherwise, the prognosis is not so good and the treatment of the latter requires additional consideration.

## ABSTRACT OF DISCUSSION

DR. WALTER BREM, Los Angeles, Cal.: For a long time I have looked on Dr. Musgrave as my master in the study of amebic infections. A monograph which he wrote with Clegg seven years ago first interested me in the subject. I feel, therefore, a certain timidity in disagreeing with Dr. Musgrave regarding the ipecac treatment of intestinal amebiasis. But, since any investigation of the treatment of intestinal amebiasis must be based on a careful study of a few selected cases over a considerable period of time following the treatment, I feel that there may be some excuse for my speaking.

In Panama, Zeiler and I treated amebic infection for four years by irrigations. We used chiefly quinin in from 1 to 2,500 to 1 to 250 solution, and thymol in from 1 to 3,000 to 1 to 1,000 solution, and quinin and thymol combined. Our results were unsatisfactory. Two years ago, after Dr. George Dock published his paper on ipecac treatment of amebic dysentery, we decided to give this method a thorough test. In our classification of cases, we considered "amebic dysentery" a chronic condition, with acute exacerbations, characterized by diarrhea and tenesmus and the presence of blood, mucus and amebas in the stools. Our criterion of cure was the eradication of the infection, and we considered this demonstrated only by repeated examinations of the stools over a reasonably long

period of time after the treatment was discontinued. We apparently cured twenty-one out of twenty-two patients treated with ipecac. About ten of these patients were followed over six months and repeated examinations of the stools were made. Several of them were followed more than a year and there was no recurrence of dysentery or reappearance of amebas.

One of our patients had amebas continuously in his stools for over two years. We tried every method known to us to rid him of the infection but failed. There were always from twenty to thirty amebas in each field of the low power lens at every examination. We finally gave this patient 120 gr. of ipecac in twenty-four hours. The amebas immediately disappeared and there has been no recurrence in over one year.

Another patient had a liver abscess three years before we saw him and had had repeated recurrences of dysentery. He also had had an appendicostomy performed seven months earlier, and at operation the cecum was found to be extensively diseased. Dysentery recurred seven months after the appendicostomy and one month after the postoperative treatment was discontinued. We then treated the patient with ipecac. He made a rapid recovery and on many examinations during five months no amebas could be found. He has remained well one and a half years.

One patient we failed to cure by giving ipecac by the mouth. He had three recurrences of dysentery, and on his last admission to the hospital he was emaciated and apparently dying. Dr. Lloyd Noland did an appendicostomy on him and found the intestine thickened and diseased. Dr. Noland kindly returned the patient to us for postoperative treatment and we introduced ipecac through the appendix. In three days the amebas had disappeared from the stools; they did not reappear, and the patient made a rapid recovery. He was kept in the hospital as an orderly so that he could be watched and frequent examinations of his stools could be made. It is now five months since treatment and he is well and no amebas can be found. The conditions of the treatment render the case one of experimental value.

We had another patient whom we failed to cure by giving ipecac by the mouth. We then gave it per rectum, suspended in starch water. There were ulcers present in the rectum and we had the satisfaction of seeing these gradually heal after the enemas were given.

There are several chances of failure in the ipecac treatment of amebic dysentery and I think that these chances of failure are responsible for the conflicting reports that come from various observers. In the first place, the ipecac may be adulterated. In the second place, the salol coating may be so thin that it is dissolved in the stomach and the ipecac vomited. Third, if the pills are too thickly coated they may pass through the intestine intact without the salol coating being dissolved at all.

Fourth, the matter of diet is important, for if food that resides long in the stomach is given before the ipecac, the latter also is held in the stomach until it is vomited. No solid food should be allowed for six hours before the administration of ipecac.

Dr. Musgrave thinks that ipecac relieves the symptoms of dysentery, and is of value for that reason. My experience leads me to believe that in addition it will eradicate the infection when properly administered—that it is a specific for intestinal amebiasis, at least in the early and moderately advanced stages.

# THE BLOOD-PRESSURE IN PNEUMONIA

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The treatment of pneumonia is still so empiric that any observations which may tend to assist in the treatment of this disease are worth reporting. A few observations on the blood-pressure in some forty-eight cases of pneumonia in adults are, for this reason, offered for consideration. The reports on the blood-pressure in pneumonia vary so greatly that there must have been heretofore great divergence in instruments used or an insufficient number of observations to enable any one to gather together into a connected whole the observations that have been made. Some observers class pneumonia as a disease with normal pressure, others as one of hypertension, and still others as one with abnormally low pressure. Giglioli reports some fifty cases measured with the Riva-Rocci instrument, and states that in favorable cases the changes in pressure were slight. In severe cases the fall at the height of the disease on the fourth or fifth day was down to 80 or 90 mm. of pressure. In fatal cases rapid fall of pressure with dilatation of the heart is recorded. Others have found that a slight hypertension occurred during the first day or so, that in serious cases there was the rapid fall, the practically normal run of pressure in favorable cases, and that in favorable cases the pressure slowly returned to normal in convalescence. A drop down to 90 mm. of mercury has been considered of serious import. Gibson of Edinburgh, in studying the relation of blood-pressure to pulse and respiration, has endeavored to make some rule that would be of assistance in the treatment of pneu-

monia, or at least could be used as a warning of a beginning lack of equilibrium in the cardiovascular circulation, or even heralding a collapse. He has concluded that as a general rule, the pressure in pneumonia is a little below normal with considerable variations throughout the course of the disease. The sudden fall of blood-pressure at the crisis has not occurred in Gibson's experience; hence, though reported by other observers, it cannot be very common. A pressure that is appreciably below normal is invariably of evil omen, and any considerable fall bodes disaster — and he sums up his experience in the following well-expressed observation:

> **When the arterial pressure expressed in millimeters of mercury does not fall below the pulse-rate expressed in beats per minute, the fact may be taken as of excellent augury, while the converse is equally true. That is, when the pulse-rate per minute is higher than the pressure of the millimeters of mercury, the equilibrium of the circulation is seriously disturbed.**

C. A. Gordon has confirmed the practical value of Gibson's rule.

The following observations in forty-eight cases of pneumonia have been taken with a Janeway apparatus in Bellevue Hospital, and there has been an endeavor to take a daily measuring of the systolic blood-pressure of each patient. This has not always been possible, but in the cases which are reported a sufficient number of observations have been taken to give a fair judgment of the condition of the pressure in the course of the disease. These cases include both bronchopneumonia and lobar pneumonia, there being eight cases of bronchopneumonia and forty of lobar pneumonia. The ages have ranged from 13 to 78 years. They have been taken as they came to the hospital, of all ages, both sexes, and all conditions of life such as are found in an active general hospital service. They include the mild and moderately severe as well as the fatal cases — those of patients who were total abstainers from the use of alcohol, who used it in moderation, and who used it to excess. Of the eleven

fatal cases which occurred, ten were among those who used alcohol, the other patient being a total abstainer. In such a small number of cases as here reported one hesitates to generalize, and one's observations must be recorded as facts and occurrences which may or may not be further corroborated. In the mild cases, in which there did not seem to be much toxemia, the disease did not seem to change the blood-pressure from the average normal in young adults, 120 to 130; it remained normal throughout their attack. In some young adults whose pulse remained below 120 and the blood-pressure remained above 105 during the disease, while there was no change at the crisis in the pressure, it fell below 100 after convalescence had set in, the pressure really being lower in convalescence than during the disease. These patients all recovered. In others the pulse remained below 120 and the blood-pressure below 105, and as soon as the crisis occurred and convalescence set in the pressure quickly and steadily rose to 120 to 130 mm. In no case did we see a sudden fall of pressure at the crisis. In some of the severe cases the blood-pressure has been low, the pulse, temperature and respiration very high, and this ratio has remained persistently throughout the disease. These are the cases in which Gibson's rule is the most noticeable and the patients are very ill and recover or die as the case may be. In those patients who recovered the pulse usually diminished in frequency before the blood-pressure rose. In some few instances the reverse occurred. In other patients neither the temperature nor the pulse ran very high, and the blood-pressure was very low, below 100; still the ratio of Gibson's rule did not point to a bad prognosis, that is, the pulse-rate remained below the millimeter pressure of mercury. These patients recovered and the pressure persisted very low in their slow convalescence. In some patients suffering from chronic nephritis, the blood-pressure remained above 150 mm. but was distinctly lowered by the pneumonia. Some of these patients

recovered and some died. In those who recovered the blood-pressure rose after the crisis. In other patients with nephritis, the blood-pressure has remained high (200 to 180) and yet the patients have died. In the cases of elderly patients with arteriosclerosis and in some cases of chronic nephritis, Gibson's rule did not hold good, and yet many of these patients died. The readings of the blood-pressure gave no hint of the cardiac failure. Taking the forty-eight patients, it is interesting to note that twenty of the forty-eight showed Gibson's rule, and of these six die. Of the twenty-eight that did not show Gibson's rule, five died. As expressed in percentages, this shows that of those who showed Gibson's rule, 42.8 per cent. died, but of those who did not show it, 17.8 per cent. died. It is interesting to note among those who showed Gibson's rule that not quite half were alcoholics, and among those who did not show it not quite three-fourths were addicted to alcohol; but then among those who did not show it are included the arteriosclerotics and the nephritics, which further disturbs the ratio of blood-pressure and pulse-rate.

In summing up the subject Janeway remarks:

**When one pictures the possible causes for variation in lobar pneumonia, the difference in individual reaction to the toxemia and in extent of lung tissue involved, the motor restlessness of some patients, the urgent dyspnea of others, and the great likelihood of an asphyxial rise of pressure where cyanosis is extreme, there is little wonder at these somewhat discordant results.**

Looking at the figures alone in print without the patients, the results do seem exceedingly variable and discordant, but from impressions made at the bed-side of watching the individual patient, of judging carefully the wisdom of this or that order for medication, and using the knowledge obtained from the blood-pressure as well as from the pulse, temperature, and respiration and general appearance of the patient, the impressions left are not so discordant as the mere grouping of types would seem. In the patients who were non-alcoholic, even

among those who had passed the resistant stage of youth, Gibson's rule seems to hold particularly true. With an undisturbed blood-pressure, and with a pulse-rate well below the millimeters of mercury, one may feel easy in mind concerning the outlook, but where the pulse-rate runs higher than the millimeters of mercury of blood-pressure, there is a very distinct warning and danger-sign that cannot be disregarded. After convalescence has set in, the pulse-rate, however low the blood-pressure may be, usually remains well below the millimeters of mercury in number. Patients who have arteriosclerosis, and who have chronic nephritis, are not apt to show Gibson's rule, but the danger of cardiac failure is none the less very great. In the eleven fatal cases here recorded, five showed Gibson's rule and six did not. One cannot, therefore, attribute the break-down of the cardio-vascular equilibrium to one cause only, as many are apt to do. We hear much of vasomotor paralysis in pneumonia and infectious disease, and the figures here presented undoubtedly show that it is common enough in pneumonia, but it is not the only cause of fatal termination. The pressure may remain up, and there may be no vasomotor paralysis until a few moments before death, and the cause of death be due to a failure of the intrinsic muscles of the heart. I have often been struck, at the necropsy of patients who had died from what seemed to me a disproportionately small amount of infection in pneumonia, with the frequency in such cases of the brown friable heart muscle which seems to be summed up pathologically as brown atrophy. The great proportion of degenerated heart muscles in alcoholics has as much influence in the increased fatality of pneumonia in these patients as vasomotor paralysis. Of the eleven fatal cases here reported, one-half showed vasomotor paralysis, and half did not. The measurement of blood-pressure, therefore, will decide often the question of whether we should look to the heart or the blood-vessels to reestablish the equilibrium of the circulation. One

hears recently a great deal about the use of epinephrin in cardiac failure in pneumonia, but unless one knows whether it is a vasomotor paralysis with a low-tension pulse, or a cardiac failure with a high-tension pulse, one certainly cannot use it intelligently, for while it is wise to give it with a low tension and it undoubtedly has done good in many cases in which this has been the factor against which the epinephrin was working, it is unquestionally poor judgment to use it with a patient whose blood-pressure is already high, and whose heart is struggling without sufficient reserve force against too great a strain. On the other hand, one sees a mixture of strychnin, camphor and alcohol given to raise a falling blood-pressure. One cannot acquiesce in the wisdom of this, for therapeutically it is a neutral mixture. The alcohol will dilate the vessels and reduce the blood-pressure vastly more than the strychnin and camphor can raise it. I have heard it reported that such a mixture had been given all day to raise the blood-pressure, and the situation save by epinephrin. One always wonders if the epinephrin would have been necessary if the alcohol had been left out. It is also a grave question whether alcohol is advisable in pneumonia until we know whether the blood-pressure is high or low, for if it is lower than normal, we certainly should not desire to further reduce it by such an effective means of lowering the blood-pressure and dilating the vessels as is alcohol. There are certainly patients with whom we are required to use all the means in our power, as camphor, strychnin, digitalis and epinephrin, to prevent a vasomotor collapse, and there are other patients with whom we must equally endeavor with vasomotor dilators to reduce the tension in the pulse to the amount against which an overstrained heart can best work and carry on its share in the equilibrium of the circulation. The blood-pressure instruments to-day are of such convenience that they offer the easy opportunity to ascertain at a visit these facts. A knowledge of the blood-pressure in pneumonia will often

be of assistance in judging of prognosis and of treatment. These are the two vital points to the patient.

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## ABSTRACT OF DISCUSSION

DR. WILDER TILESTON, New Haven, Conn.: With regard to the blood-pressure in cases of pneumonia, I do not think it has much value in prognosis. At a recent meeting of the American Society for the Advancement of Clinical Investigation Dr. Sailer reported the results of a study of the blood-pressure in pneumonia, and he found that most cases of patients who died did not follow Gibson's rule. I do not think that sufficient data have been accumulated to lay down definite rules regarding the importance of the blood-pressure in determining the prognosis in pneumonia.

# IMMUNO-DIAGNOSTICS IN INTERNAL MEDICINE

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In the presence of infection certain reaction products are developed in the infected individual. Their development is excited by the infective bacteria. This immunizing process may be due to the action of the cells or of the fluids or of both. If the process more particularly affects the cells the result is termed cellular immunity; if it affects the fluids, humoral immunity. Some of the substances formed are protective to the individual; others apparently have little demonstrable protective influence, and still others sensitize the subject. The substances formed in humoral immunity may be divided into: (1) agglutinins, (2) precipitins, (3) complement-binding substances and (4) opsonins.

The demonstration of these substances forms the basis of the serum reactions which have attained so much importance in recent years. The detection of agglutinins attained its greatest importance in the diagnosis of infections caused by typhoid, paratyphoid, and colon bacilli, in which they are specific. Strictly speaking, the latter term must be used in a relative sense, as normal serums possess a certain amount of agglutinins and it is only their demonstration in relatively high dilution that renders the reaction specific.

The complement-binding principle of Bordet has received many applications to diagnosis, the most important of which is the serum diagnosis of syphilis. While numerous modifications of this method have been pro-

posed, the original method of Wassermann still remains the most reliable. While the test requires for its proper performance the skill of a trained laboratory worker, the interpretation of the results should always be in the hands of the clinician, who should possess for this purpose a broad knowledge of immuno-diagnostics. This test is not only useful for the initial diagnosis of syphilis or for determining the presence of that disease in doubtful cases, but it has many applications as an aid to prognosis and treatment during the course of the affection.

It is quite remarkable that this reaction is not more frequently employed in controlling the treatment and management of syphilitics. One of the strongest claims for the specificity of salvarsan was the fact that it converted positive Wassermann reactions into negative ones. I am fully convinced that if syphilitics were properly managed in this age, serious recurrences and parasyphilitic diseases would be reduced to a minimum.

However, when used to control the treatment of syphilitics, this reaction should be properly understood. One negative reaction does not mean that the patient has been cured of syphilis. This, unfortunately, has been considered sufficient, especially since the introduction of salvarsan. Just how often a patient should be examined after giving a negative reaction will of necessity remain more or less speculative. In the first year I should not regard a negative reaction as an indication to suspend treatment, but I should wish to know by an occasional examination, say every other three months, whether the reaction was still negative; in other words, whether the treatment was being pushed sufficiently. This would apply equally in the second year, with but few and short intermissions of treatment. The intermissions might be lengthened in the third and fourth years. Every time the reaction is found it means, as pointed out in my first paper,[1] active syphilis; and calls

1. Butler: Serum Diagnosis of Syphilis, New York Med. Jour., Nov. 30, 1907.

for specific treatment. When the reaction persists under treatment over an indefinite period, it means active lues with all its possibilities and its resistance to treatment.

Passing over the various applications of this and similar principles to the diagnosis of such diseases as echinococcus infection, cancer, etc., I wish to take up the consideration of the diagnosis of tuberculosis by means of immuno-reactions and particularly by an application of the complement-binding principle.

Interest in the tuberculin reaction has been materially increased since the discovery of Pirquet, who found that individuals who had once suffered from a tuberculous infection or were at the time affected with tuberculosis, would react locally to the application of Old Tuberculin by the method of vaccination. This reaction is the first example of the use of such immuno-diagnostic methods for the diagnosis of tuberculosis. Following this discovery of Pirquet, a variety of vaccination methods have been devised, such as vaccination in the conjunctiva, hence the ophthalmic reaction, the percutaneous method, etc.

In regard to the subcutaneous reaction, some interesting observations were published by Franz. He found, on examining 400 men of a Bosnia regiment which came from a tuberculous district and whose members were in the first year of the service, that 61 per cent. reacted positively to Old Tuberculin. He examined a Hungarian regiment from a section with little tuberculosis and found that 38 per cent. of them gave positive results. Only a small number of the reacting individuals were demonstrably tuberculous, while a number of the non-reacting individuals were tuberculous. While these statistics might argue strongly against the specificity of the tuberculin subcutaneous reaction, there is no doubt of its value in suspected tuberculous cases in the hands of competent observers. We may say that whatever the subcutaneous method lacks in decisive diag-

nostic value for tuberculosis, the other methods do not possess; notwithstanding this, great claims are made for the efficiency of the ophthalmic reaction in active tuberculosis. There is, likewise, no doubt of its being a valuable aid in the diagnosis of tuberculosis; that it is not a decisive differential diagnostic recourse is generally recognized.

The skin reaction of Pirquet is a specific tuberculin reaction, but the tuberculous process may have healed out years before; as a consequence, this test is of little value in diagnosing an active process, except during infancy, although a strong reaction may at times lend additional weight to a diagnosis.

The occasional unfavorable effects of the subcutaneous injection of Old Tuberculin, together with the uncertain value of tuberculin reactions, show the desirability of a test devoid of these two objections. Efforts have already been made in this direction. They have been directed toward the demonstration of specific substances in the blood of tuberculous patients. The antibodies that have been investigated are agglutinins and complement-binding substances. Arloing and Courmont were the first to report on agglutinins in tuberculous cases. They found that the serum and serous exudates of many tuberculous patients agglutinated tubercle bacilli. This serum test has not been much tried out, evidently because it has fallen short of tuberculin reactions in simplicity and results.

Bordet, in his studies of Pfeiffer's phenomenon, discovered a new principle in immunity, namely, that of complement fixation. He was able to show by an indirect method, in which a hemolytic system was employed, the presence of complement-binding antibodies.

By means of this method he found that the blood of guinea-pigs which had been immunized with killed tubercle bacilli contained an antibody that would unite with an emulsion of tubercle bacilli as antigen and bind complement.

The discovery of Bordet opened up a great field for investigation into the presence of antibodies in body fluids by this method, and from this investigation the syphilis rection ultimately developed.

Wassermann and Bruck investigated extracts of tuberculous tissue for tuberculin and antituberculin and found both. They believed that there existed a direct association between tuberculin treatment and antituberculin in the blood of tuberculous patients. They observed that tuberculous individuals who had no complement-binding antibodies reacted strongly to tuberculin, while those that had them failed to do so. From this, Wassermann originated an ingenious theory in explanation of the tuberculin reaction. He asserted that when antituberculin was present, it neutralized injected tuberculin and consequently no reaction occurred. If it was not present the circulating injected tuberculin was attracted into the diseased focus by antituberculin, with which it united and took up complement, thus causing local congestion and the general reaction.

Wassermann's and Bruck's experiments were confirmed by Lüdke and Citron; other workers, however, were unable to do so. Weil and Strauss, Czastka, Wolf-Eisner and Ascher, Cohn, and Butler and Mefford were unable to find any parallelism between complement-binding antibodies and tuberculin reactions, or between opsonins and the latter. All seem agreed, however, that they were able in a considerable number of cases to show complement-binding antibodies in the serum of tuberculous patients.

In association with my assistants, Drs. William E. Putz and Nora Johnson, I have undertaken an investigation into the serum diagnosis of tuberculosis on the basis of complement deviation. The majority of the patients were selected from the second and third stages of the disease, including, however, a number of suspected cases.

The technic employed in this work is that used for complement-deviation reactions. For antigens, the

various tuberculins were used, including bacilli emulsion. Old human tuberculin was chiefly used. My previous experiences with it were not satisfactory; in fact, its action at times was so erratic as to raise the question of specificity of the reaction.

To avoid this difficulty in subsequent experiments we used human bacilli emulsion as antigen. It is necessary to titrate it carefully and also to repeat titrations before each test in order that it shall not be used in more than half the amount of inhibiting quantities. We also used bovine bacilli emulsion, titrating it in the same manner.

The serums are obtained in the usual way and inactivated to 56 C. for one-half hour. This is absolutely essential, as we convinced ourselves that active serums could not be used for this reaction. And as a matter of fact, the original reaction calls for inactivation. Active serums frequently contain anticomplementary substances. They may show inhibiting properties without the antigen. In the presence of antigen this may be increased evidently from a summation of inhibiting factors.

In regard to the employment of active serums for their complement, we can also state from experience that the content in complement of different serums is variable and absolutely unsuitable for the reaction.

In our first examinations we put through three different tests with all serums. In the first the serums were inactivated and guinea-pig serum added for complement. In the second the serums were not inactivated, but fresh guinea-pig serum was also added. In the third the serums were used in active state, but no additional complement was used.

We found that the first series would work out satisfactorily, the second series was erratic on account of anticomplementary substances, above referred to, and the third series showed little or no hemolysis in practically all tubes.

Fresh guinea-pig serum was used as complement and rabbit antisheep amboceptor and sheep's corpuscles were employed as the hemolytic system. Emory speaks of non-tuberculous serums anchoring complement in the presence of bacilli emulsion, the chief difference between non-tuberculous and tuberculous serums being in the latter absorbing complement in shorter time. We are not able to confirm this observation.

The protocol of a reaction would read as follows:

| T. B. Bacilli Emulsion | Patient's Serum | Guinea-Pig Serum | Anti-Sheep Amboceptor | Sheep Corpuscles, 5% Suspension | Hemolysis? |
|---|---|---|---|---|---|
| 0.05 | 0.1 | 0.1 | 0.002 | 1 | No |
| 0.05 | 0.2 | 0.1 | 0.002 | 1 | No |
| 0.025 | 0.1 | 0.1 | 0.002 | 1 | No |
| 0.025 | 0.2 | 0.1 | 0.002 | 1 | No |
| 0.05 | ... | 0.1 | 0.002 | 1 | Yes |
| 0.025 | ... | 0.1 | 0.002 | 1 | Yes |
| .... | 0.4 | 0.1 | 0.002 | 1 | Yes |

The quantity of antigen and amboceptor employed are, of course, variable and depend entirely on their strength. It is necessary to titrate the antigen and amboceptor before each test. Therefore, the above is simply a diagramatic representation of the amounts used.

The amboceptor should be used in twice the strength sufficient to hemolyze the corpuscles in fifteen to twenty minutes.

In making the reaction, the tubes must be closely watched after being finally placed in an incubator. A reading should be made as soon as the controls on the hemolytic system, tuberculin and a few known controls hemolyze. The degree of inhibition of hemolysis varies from 1 to 4. Eventually in practically all instances the hemolysis will be complete, but the delay in hemolysis with tuberculous serums is striking in contrast to the promptness with which the controls hemolyze.

We examined the serums of 100 cases. Sixty-five of these were tuberculous or suspects. The remainder were control cases, consisting chiefly of acute infections, as pneumonia, erysipelas, typhoid fever, catarrhal jaundice,

influenza, etc. The patients from whom the specimens of blood were obtained were in the tuberculous department and medical wards of the Cook County Hospital and in my Willard Hospital clinic.

Of the tuberculous cases, 72 per cent. gave a positive reaction with human tubercle bacilli emulsion as antigen and 23 per cent. gave a positive result with bovine emulsion as antigen; in only one instance did we get a reaction with bovine emulsion and not with human. Of the thirty-five controls, three gave a reaction with human tubercle bacilli emulsion. One of them was a pneumonia, another an influenza and the third case was one of rheumatism. One control gave a reaction with the bovine emulsion.

In one case of cancer and one of chronic nephritis, the heated serums as well as the inactivated serums with antigen inhibited hemolysis to some extent. This is an experience, above referred to, that we frequently observed with active serums in general and not infrequently in cancer serums which had been inactivated.

Recollecting what the first experiences with the lues reaction were, we have every reason to feel encouraged with these results and fully believe that this reaction will be brought to a high degree of efficiency in the diagnosis of tuberculosis.

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## ABSTRACT OF DISCUSSION

DR. F. M. POTTENGER, Monrovia, Cal.: It is very interesting to note the difference in the attitude of both the profession and laymen toward the two diseases, syphilis and tuberculosis. If a Wassermann is found on a patient he is willing, and is at once advised to have treatment for syphilis. If a positive tuberculin test is found, in the absence of clinical symptoms, we simply say that an infection is present, but as a rule take no steps to cure it. I believe that the time will soon come and is now almost here when the treatment of tuberculosis will consist in hunting out these early infections and treating them without delay. We know that practically every child is infected with tuberculosis before his fifteenth year. If these cases were sought out at this time they could easily

be healed and the healing would result, according to animal experimentation, in a considerable degree of immunity, which would protect the patient in after years. I believe the future cure of tuberculosis will consist in early diagnosis and early treatment and that it will fall into the hands of those who treat children's diseases. If we are successful in our efforts to cure tuberculosis we must employ every means possible to diagnose and treat the disease early. I hope that Dr. Butler's method will be able to show definitely the presence or absence of active tuberculosis. If so it will be a great advance.

DR. WILLIAM J. BUTLER, Chicago: In the employment of the tuberculin reactions, with the exception of the subcutaneous test, we should remember that they are not decisive diagnostic tests for active tuberculosis. We can also say that the subcutaneous test, where positive, is not decisive unless we can demonstrate evidences of activity in the suspected focus of infection. The statistics of Franz, above cited, as well as personal experience, substantiate the latter statement. Individuals with healed-out foci of tuberculosis may react positively to any method of inoculation with tuberculin. Under these conditions a positive reaction would not mean active tuberculosis and would not therefore call for treatment. In view of the fact that the tuberculin reactions are not decisive differential diagnostic measures, except under the conditions above mentioned, it is hoped that the investigations into the antibody content of the blood during an active immunizing process, that is, active tuberculosis, may help to dispel the present uncertainties.

# INFANTILISM IN PITUITARY DISEASE*

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Since the appearance of Fröhlich's paper[1] in 1901, it has become generally recognized that tumors in or near the pituitary gland may cause disturbances of body growth and general metabolism which are quite distinct from acromegaly and gigantism. Frankl- Hochwart[2] has recently collected and analyzed the findings in 155 pituitary affections of this character. The symptoms present may be roughly divided into two classes: those due to the mechanical effects of the tumor and those which seem to be due to an altered internal secretion. To the former group belong the headache, vomiting and visual disturbances. The most characteristic of these, primary optic atrophy and unilateral or bilateral temporal hemianopsia, are due to direct pressure on the optic chiasm or nerves. To the latter group belong the sexual disturbances (retarded sexual development, cessation of menses, etc.), the obesity, the stunted growth, and possibly the occasional diabetes insipidus. These are due, in part at least, to a diminished secretion of the anterior lobe of the gland (hypopituitarism).[3]

## REPORT OF CASES

Owing to the general interest in this group of conditions and to the fact that they are probably more common than is generally supposed, it seems advisable to report the following case histories, even though the diagnoses were not confirmed at autopsy or operation. The clinical pictures presented by the first two patients are so characteristic as to leave little doubt concerning the nature of the trouble. The third, a doubtful case, is reported because the effect of lesser changes in the pituitary secre-

*From the Department of Internal Medicine, University of Michigan.

1. Fröhlich, Alfred: Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie, Wien. klin. Rundschau, 1901, xv, 883, 906.

2. Frankl-Hochwart, L., v.: Die Diagnostik der Hypophysistumoren ohne Akromegalia, Wien. med. Wchnschr., 1909, lix, 2127, 2258, 2326.

3. Cushing, H.: Partial Hypophysectomy for Acromegaly, Am. Surg., 1909, cl, 1002; Biedl, A.: Innere Sekretion, Berlin and Wien, 1910.

tion is but little understood and because it is probable that in this patient we are dealing with a mild form of chronic hypopituitarism.

CASE 1.—*History of brain tumor. Blindness due to primary optic atrophy. Retarded growth. Sexual infantilism. Obesity. Diabetes insipidus.*

*History.*—The patient was a young man, aged about 27; family history negative. Between the ages of 5 and 9 years he had the typical symptoms of brain tumor, with severe headaches, vomiting, marked emaciation, and gradually developing dimness of vision which progressed to complete blindness. At this time also he began to suffer from polyuria. At about the age of 9 the headaches and vomiting disappeared, the patient began to increase in weight, and since that time he has been excessively fat. He has never shown the slightest indications of sexual development.

*Examination.*—The patient presented the general appearance of a blind, fat boy (Fig. 1); height in stocking-feet 4 ft. 9½ in.; head fairly large; supra-orbital ridges not well developed; lower jaw rather small. The teeth were crowded together on both jaws. No marked disproportion existed between the length of the body and that of the extremities. There was marked genu valgum (Fig. 2). The hands were small and chubby, with delicate tapering fingers (Fig. 4). The feet were also very small and there was flat-foot on both sides.

The fat over the whole body was increased, the weight being 166½ pounds. Deposits of fat were especially marked in the mammæ, buttocks, abdomen, and above the symphysis pubis (Figs. 1, 2, 3). These gave the figure a feminine appearance. The penis was very small and almost covered by the mass of fat about the mons veneris. The scrotum was small and buried in fat. Both testicles were of infantile type, the left being descended normally, the right felt at the external ring.

The hair over the head was normal; over the body, it was very fine and soft. No beard had ever developed and only a few coarse hairs were present in the axillæ and about the pubes. The skin was soft and delicate. The voice was high-pitched and of a melodious quality. The patient presented many emotional characteristics of childhood, being affectionate, buoyant, but inclined at times to discouragement and weeping spells. His general intelligence and intellectual development were good, and, in spite of his blindness, he was able to manage a small business very successfully.

Since childhood the urine had always been increased in amount; at times, according to the patient's statements, reaching eight or more quarts a day. Repeated examinations of the urine showed a specific gravity which did not vary from 1,003 to 1,004. The urinary examinations were otherwise negative.

The eyes were completely blind. An examination showed: "Both pupils slightly dilated, the left one more than the right. Neither react to light, the light perception being *nil*. Some nystagmus is present, probably due to inability to fix objects. Extrinsic eye-muscles normal. Ophthalmologic examination shows clear media. The fundus is somewhat over-pigmented, but probably not pathologically so. Both nerve-heads show clear margins and are bluish-white in color. The objective picture is that commonly seen in primary optic atrophy. The vessels show no evidence of pressure."

Two attempts were made to obtain radiographs of the skull but the plates were not good. As the patient complained of headache after having been exposed to the *x*-ray, no further efforts in this direction were made. Plates of the hands showed complete fusion of the metacarpal and phalangeal epiphyses. The lower epiphyses of the ulnar and radius were also fused but the lines of fusion were plainly visible and were indicated by notches on the edges of the radii so that the fusion was probably recent and considerably delayed beyond the normal.[4]

The history of brain tumor, the stunted growth, optic atrophy, obesity, sexual infantilism and diabetes insipidus leave no doubt as to the presence of a tumor in or near the pituitary gland producing symptoms recently attributed to hypopituitarism. The patient took the powdered anterior lobe of the hypophysis, 15 gr. (1 gm.) a day, for over a month but without marked effect. More recently he has been given the powdered thyroid glands, but after about two weeks he complained of pains in the head, dizziness and apprehensive sensations which led to a discontinuance of the medication.

CASE 2.—*Since the age of 13, periodic headaches with vomiting. Mild sexual infantilism. Adolescent height and figure. Bitemporal hemianopsia, with primary optic atrophy. Bony changes in the region of the sella turcica.*

*History.*—A man, aged 40, first entered the University Hospital at Ann Arbor, July 7, 1910, complaining of dimness of vision, constipation, palpitation of the heart and general weakness. His family history was negative, except that one sister was suffering from a nervous trouble. Patient had had the ordinary diseases of childhood. He denied venereal infection. As a child he had gone to school and had had no difficulty in keeping up with his classes. At about the age of 13 he began to suffer from periodic headaches which were usually associated with vomiting, coming on one or two hours after the onset of the headaches. These headaches often seemed to be precipitated by hard work, but they came at fairly regular intervals of one to two months. His habits had been good; he had used alcohol rarely and had not used tobacco, tea, or coffee. He had had occasional nocturnal emissions between the ages of 14 and 20, but none since then. He had never married and had never had sexual intercourse.

The present trouble, in his opinion, dated back three or four years. During this time the headaches had increased greatly in severity, but the associated vomiting had lessened so that at the time of admission he rarely vomited. The headaches usually centered about the frontal region, extending down over the eyes. His sight began to fail about two years previously and the failure had gradually increased. He had become constipated, nervous, and inclined to isolation. Six years before he was advised to drink large quantities of water and he believed that in the last year he had been unusually thirsty. The patient

4. Rotch, T. M., and Smith, H. W.: A Study of the Development of the Epiphyses of the Hand and Wrist for the Purpose of Classifying the Cadets at Annapolis, Tr. Assn. Am. Phys., 1910, xxv, 200.

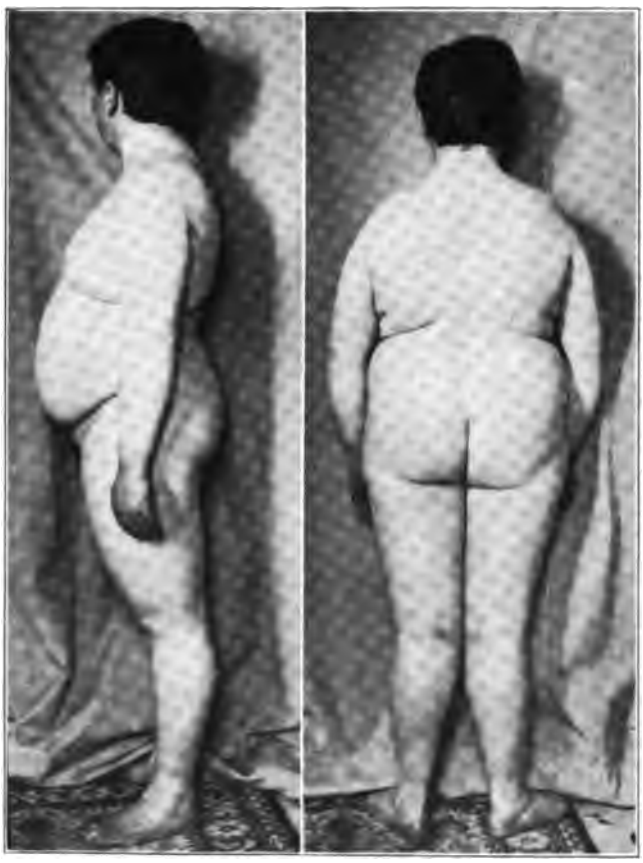

Fig. 1.—Lateral view of patient 1. Note the obesity, lumbar lordosis, small hands and feet.

Fig. 2.—Posterior view of patient 1. Notice the genu valgum and the distribution of fat on the body.

**Fig. 3.—Anterior view of patient 1. Notice the distribution of fat.**

Fig. 4.—Hand of patient 1 (to the left).—Compared with hand taking a No. 7 glove. Note the small size, the tapering fingers and the delicate skin.

Fig. 5.—Anterior view of patient, Case 2, by the side of a man 5 feet 8 inches high. Note the adolescent figure and the absence of hair on the face and pubic region.

Fig. 6.—Patient 2, lateral view.

Fig. 7.—Hands of patient, Case 2. Note the long slender fingers and dry skin.

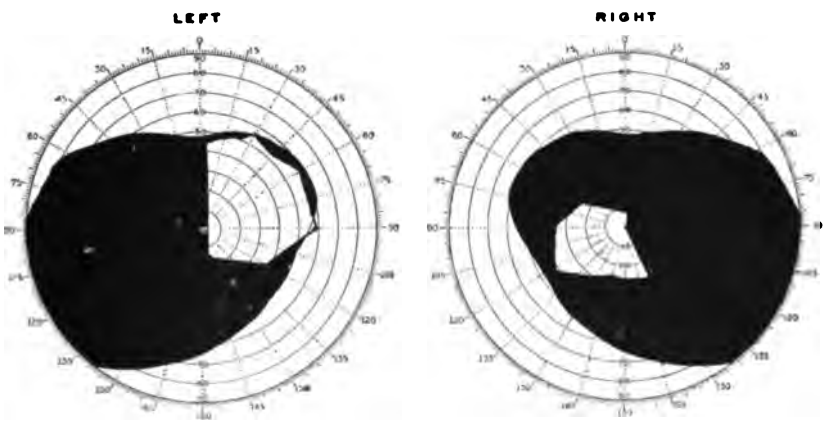


Fig. 8.—Visual fields for candle light in second case, showing the bitemporal hemianopsia.

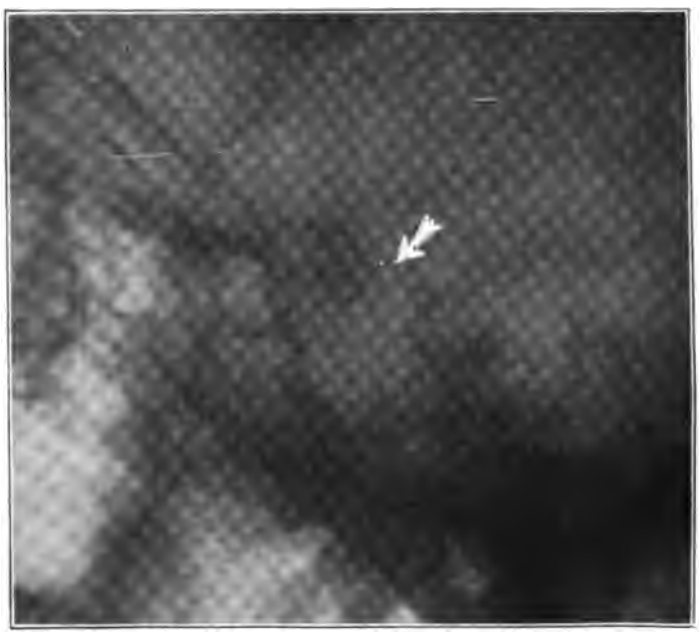

Fig. 9.—X-ray plate of the base of the skull, Case 2, showing absence of normal outlines of sella turcica. The arrow points to the sella region and it is possible that the large pale area represents the abnormal sella (natural size).

Fig. 10.—Anterior view of third patient showing small figure and wrinkled skin.

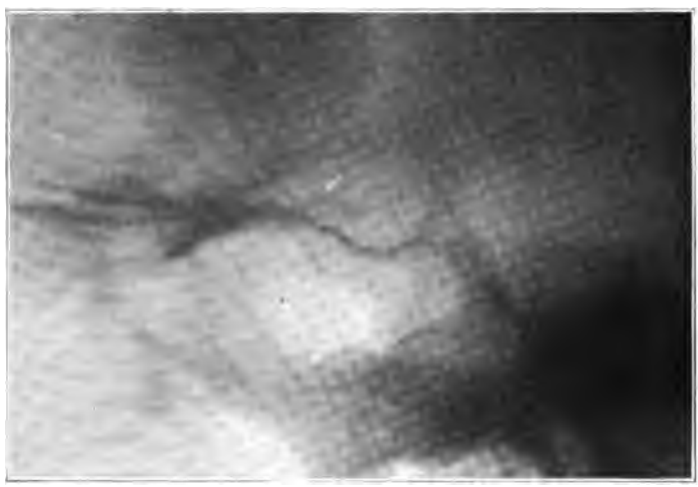

Fig. 11.—Skull of third patient, showing, enlargement of the sella turcica cavity, with a wide entrance above (natural size). The arrow within the cavity points to the region of the tuberculum sellæ. Ordinarily the shadow of the tubercle rises abruptly and joins that of the anterior clinoid process, giving a vertical shadow to the anterior wall of the cavity. Here, however, the flattening of the tubercle gives a pointed appearance to the anterior end of the cavity. The plate resembles that taken after death from the prepared skull of Erdheim's first patient, but in my case the sella is larger and the flattening of the tubercle more pronounced. (Erdheim, J.: Ueber Hypophysenganggeschwülste und Hirncholesteatome. Sitzungsb. d. k. Akad. Wissensch. Math-naturw. Kl., 1904, cxiii, Part 3, p. 710.)

left the hospital July 13, but returned Nov. 19, 1910, stating that his headaches had become more troublesome and that he had had some discomfort in the epigastrium without nausea or vomiting. His sight had fluctuated considerably, but had become worse on the whole.

*Examination.*—Dec. 2, 1910, the patient appeared to be a short, slender and delicately proportioned man with a figure resembling that of a male adolescent (Figs. 5 and 6). Height in stocking-feet was 5 feet 2 inches, weighed 76 pounds. The head was well formed, the thoracic spine showed a slight kyphosis, the hands (Fig. 7) and feet were relatively long and slender. The skin over the face and hands was sallow, yellowish, dry and scaling; over the covered parts of the body it was soft and rather delicate. The cheeks and lips showed a few thin, colorless hairs; the hair over the body was fine and colorless; and there was almost an entire absence of axillary and pubic hairs. The penis appeared normal; the testicles were small and rather soft. The patient seemed nervous and emotional. The pupils were equal and reacted well to light and moderately well on accommodation, there being no paralysis of the extra-ocular muscles. The vision was so diminished that the patient could hardly count fingers. Ophthalmoscopic examination in the university eye clinic showed a primary-optic atrophy. The visual fields, as determined by a lighted candle, showed a bitemporal hemianopsia (Fig. 8). The general strength was diminished but there was no definite paralysis and no disturbances of cutaneous sensation. The tendon reflexes were everywhere active, the skin reflexes not increased. The thyroid gland was neither seen nor felt. Lungs, heart, and abdomen were negative. A single blood-pressure determination on the first admission gave a systolic pressure of 110, but on the second admission it was taken repeatedly and was constantly low, ranging from 84 to 87. Wassermann reaction, gastric analyses, and microscopic stool examinations were negative. The urine, of which 1 to 2 liters were passed daily, showed a constantly low specific gravity, the average of twelve examinations being 1,006, with 1,004 and 1,010 as extremes. A restriction of liquids for a week did not raise the specific gravity. Two radiographic plates (Fig. 9) taken transversely across the head showed an absence of the shadows normally cast by the bones surrounding the sella turcica. Plates of the hands, wrists, elbows and knees showed completed fusion of the epiphyses. The possibilities of operation were discussed with the patient but he declined on account of the danger and our inability to promise a restoration of sight.

CASE 3.—*Retarded sexual development. Small frame. Large sella turcica.*

*History.*—A man, aged 52, came to the University Hospital at Ann Arbor April 24, 1911, complaining of stomach trouble. His family history was negative. He had four brothers, all of whom were of average height, ranging from 5 feet 7 inches to 5 feet 9 inches. The patient had never been very robust. Up to the age of 16 he had progressed normally in school but at that time he had an illness which was diagnosed as spinal meningitis and which interrupted his schooling. His first definite sexual feelings and first seminal emissions occurred at about the age of 30 years. This was followed by a period of masturbation, and since then by subnormal sexual impulses. The patient had never married

and had never had sexual intercourse. He had always had more or less indigestion with intestinal disturbances. He was in the hospital in 1906, at which time the diagnosis was made of neurasthenia, chronic gastritis, pigeon breast, and ulcerated septum. He entered again on account of epigastric distress after meals, belching of gas, and irregularity of bowels. Physical and laboratory examinations failed to show any definite organic cause for these complaints.

*Examination.*—The patient was a short man, 5 feet 2½ inches in his stocking-feet, weight 91½ pounds without clothes (Fig. 10). Like the preceding patient he was delicately built; the bones were small and slender; the hands relatively long and slender. The chest was rounded and was asymetrical, with a markedly protruding sternum. There was slight kyphosis in the upper thoracic spine. The skin of the face was deeply tanned and much wrinkled. The hands were cyanotic. The skin over the exposed parts of the body was dry and scaly; over the covered parts normal. The growth of hair was normal; the external genitalia rather small; knee-jerks were active; Wassermann reaction negative. The specific gravity of the urine was 1,012; quantity was not increased. Examination of the eyes in the eye department of the University Hospital showed a slight general limitation of the visual fields due to cortical cataracts. The optic nerves were rather pale, with arteriovenous compression. A radiograph of the skull showed a sella turcica somewhat larger than normal and characterized especially by an absence of the shadow of the tuberculum sellæ, and by a wide entrance from above into the fossa (Fig. 11).

We are indebted to the French school for numerous studies and discussions on the nature of infantilism. Various definitions for the condition have been proposed. Some would limit it to the persistence of childish or infantile characteristics in older people, while others prefer the more general conception of a "persistence in a given person of characteristics, bodily and mental, which belong to one of less advanced age." The Brissaud type of infantilism in which the characteristics of infancy or early childhood are especially retained is described as follows: "Round, chubby face, lips projecting and plump, small nose, smooth face, fine clear skin, fine hair, eyebrows and eyelashes scant, eyes prominent, large round cheeks, infantile face and head, skeleton under-developed, neck short and chubby, body long and cylindrical, abdomen prominent, limbs round and large, layer of fat over the whole body, infantile pelvis, lumbar lordosis, rudimentary sexual organs, no hair except on head, high-pitched voice, thyroid small, mind slow, retardation of ossification, absence or retardation of second dentition." My first patient showed many points in common with this description of the Brissaud type of infantilism.[5] In him development had been arrested early in life and he showed many of

5. Brissaud: L'infantilisme vrai, Nouv. iconog. de la Salpêtrière, 1907, xx.

the bodily, mental and sexual characteristics of childhood. Brissaud would attribute such arrested development to an insufficient thyroid secretion, but it seems certain that this conception is too restricted and that other causes may be operative. So far as hypopituitarism is concerned it is possible, of course, that this may influence the thyroid secretion or that it may be secondary to a thyroid disease, for the two glands bear an intimate relation to each other. According to Frankl-Hochwart, however, constant anatomic changes have not been demonstrated in the thyroids of patients with this type of pituitary disease, and the unusual intelligence of the first patient would speak against a marked thyroid insufficiency in his case.

The bodily development of the second patient differed from that of the first chiefly in the absence of obesity and in the general appearance of adolescence rather than of childhood. The infantilism in this case bore a general resemblance to that which usually goes under the name of the Lorain type, and has been described as follows: "Small stature, delicately-formed, slender skeleton, skin soft and pale, large shoulders, lower extremities long and slender, trunk relatively small, infantile sternum and pelvis, epiphyses normally united, no fat, abdomen normal, finely chiseled face, voice high, neck long, genital atrophy, absence of or slight secondary sexual characteristics." It has been claimed that these two types of infantilism are essentially different and that in the Brissaud, the fusion of the epiphyses is delayed, while in the Lorain type the fusion occurs at the normal time or prematurely. The value of this criterion has been shaken by the fact that in some cases of the Lorain type epiphyseal fusion has been retarded.[6] It would seem that the two are not essentially different but that in the Brissaud type development is arrested at an earlier stage than in the Lorain type, due either to an earlier onset or to a more severe causative agency.

The Lorain type of infantilism appears to be rather unusual in pituitary disease, possibly on account of the frequent development of obesity which would mask its characteristic features. However, in one of Levi's[6] patients and in that described by Lemann and Van Wart,[6] typical Lorain infantilism was associated with presumable disease of the pituitary gland. It is important to note this occurrence because it serves to indicate

6. Levi, E.: Contribution a l'etude de l'infantislisme de type Lorain, Nouv. iconog. de la Salpêtrière, 1908, xxi, 297. Lemann, Isaac I., and Van Wart, Roy M.: A Case of Infantilism with Absence of Thyroid and Tumor of Pituitary, THE ARCHIVES INT. MED., 1910, v, 519.

that the same group of causes may give rise to the different types of infantilism. Frankl-Hochwart believes that when pituitary disease occurs in early life obesity is more common than when it begins later, but this rule is subject to numerous exceptions. In my second patient a mild type of hypopituitarism occurring just before adolescence was probably sufficient to stunt the growth and to retard sexual development without inducing obesity. In the third patient the diagnosis is not well established, but the enlargement of the sella turcica and the general resemblance to the second patient suggest that we are dealing here with a mild form of hypopituitarism.

The first patient showed a typical diabetes insipidus, with very large quantities of urine and a constantly low specific gravity. Frankl-Hochwart found this condition mentioned in 7 per cent. of the cases which he investigated. On the other hand, diabetes mellitus was very rare in his series, much more so than among the collected cases of acromegaly.

We are quite ignorant as to the precise nature of the diabetes insipidus which occurs in pituitary disease. It has been shown that the posterior and middle lobes of the gland may increase the flow of urine,[7] and it is possible that an overaction of this portion of the gland may be associated with a diminished activity of the anterior lobe. Possibly, however, the diabetes insipidus results from nervous impulses excited by an irritation of structures at the base of the brain. In my second case, the urine was not increased markedly in amount, varying between 1 and 2 liters per day during his stay in the hospital. The examinations, however, were interesting in that they showed a constantly low specific gravity which averaged 1,006 and never exceeded 1,010. E. Meyer[8] has shown that in true diabetes insipidus the kidney is unable to secrete concentrated urine, and I found that even though this patient took less than 500 c.c. of liquid per day, the specific gravity of his urine was not raised. Unfortunately it was not possible to make an accurate metabolic study.

## CONCLUSIONS

1. The infantilism associated with disease in or near the pituitary gland may resemble either the Brissaud or the Lorain type of infantilism.

2. A constantly low specific gravity of the urine in patients with such disease may be the equivalent of a mild diabetes insipidus.

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7. Schäfer: The Functions of the Pituitary Body, Proc. Roy. Soc. Biol., lxxxi. 442.

8. Meyer, E.: Ueber Diabetes insipidus und andere Polyurien, Deutsch. Arch. f. klin. Med., 1904, lxxxiii, 1.

# MYATONIA CONGENITA: A REPORT OF A CASE WITH AUTOPSY

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Oppenheim[1] described in 1900 a remarkable disease in children the chief symptom in which is a hypotonia or even atonia of the muscles, combined with a corresponding diminution of the tendon reflexes. There is limitation of active movement varying in degree. In the most marked cases the extremities lie motionless and apparently paralyzed. On close observation contractions may be brought out in some or many of the muscles, but these are weak and without locomotor effect. In one of his cases the affection involved not only the muscles of the extremities, but those if the neck and trunk also. The condition is always more marked in the lower than in the upper extremities and the muscles supplied by the cranial nerves are not affected. Electrical stimulation shows a quantitative diminution of contractility up to its complete disappearance. There is no reaction of degeneration and no loss of sensibility. The joints are abnormally movable owing to the flaccidity of the muscles. It is a congenital affection, but it does not usually attract attention immediately after birth. He considers that it consists essentially in a retarded development of the muscles, and it tends to betterment or recovery. He did not, however, exclude the possibility of an involvement of the nerves or of the anterior horn cells. The muscles may be flaccid and soft, but they are never atrophied.

CASE.—*History.*—M. G., aged 6 months. The father was addicted to alcohol and was intoxicated at the time of conception and at intervals during the mother's pregnancy. During pregnancy the mother was well, but much worried and distracted over her husband's condition. There have been no miscarriages. The child of a previous pregnancy is healthy. The previous history of the mother is negative. The child, male, was born normally April 3, 1910. Fetal movements were felt during pregnancy and were quite as lively as those of the normal baby of the previous pregnancy. When the baby was three weeks old, the mother noticed that he seemed unusually limp, but was re-assured by the obstetric nurse in charge. When six weeks old, the mother noticed a dropping of one hand and that the hands seemed weak and limp and were not moved as freely as they ought to be. At this time she consulted a physician who said the condition was

due to weakness, that the breast milk was probably not agreeing with the baby and advised that it be taken off the breast. When the baby was two months old he was seen by Dr. Howland of New York who noted a marked atrophy of the muscles of the trunk and extremities, and deformity of the chest. The baby seemed to improve somewhat, at one time being able to move his arms, but later this power disappeared. He has never been able to move his legs at the hips, knees or ankles, but could make slight movements of the toes and fingers. He has never been able to sit up or to hold up the head. The mental development is normal. The breathing has been labored since the baby was three weeks old and this has grown progressively worse. On September 3 the baby caught cold and since then the trouble in breathing became worse, with choking spells from mucus accumulation. To give relief the adenoids were removed on September 24. The breathing was somewhat improved by the operation, but has lately become as bad as before. The weakness increased until he could no longer nurse from the breast or bottle and has to be fed with a spoon. The baby gained weight up to the time of the adenoid operation, but since then has lost.

*Physical Examination.*—October 3. Poorly developed and poorly nourished baby. The cranium was square, the forehead prominent; the fontanels depressed but of normal size; the mouth, tongue and throat were normal. There were no teeth. The pupils were equal and reacted normally. The respiration was irregular, labored and wholly diaphragmatic, but not notably accelerated. The chest showed marked increase in anteroposterior diameter. The heart, lungs, and abdomen were normal. The baby was entirely unable to hold up his head and there seemed to be a complete flaccid paralysis of the trapezius muscle. The upper extremities were not moved at all from the shoulder and very feebly at the elbow and wrist. The hands hung over in flexion when the arm was held upright. There appeared to be a flaccid paralysis of the shoulder girdle muscles with marked atrophy, particularly of the pectoralis. There was slight atrophy of the muscles of the extremities. The knee-jerk was absent.

From this time until death, October 23, the condition gradually became worse, although there were temporary ameliorations. There was increase in the mucus accumulations and in the fits of choking, and the child died in one of these attacks.

*Autopsy.*—The body was that of a somewhat emaciated, male infant; the body length corresponding to age; the weight below the average; no rash on surface of the body; all the tissues were very soft and flabby to the touch; no rigor mortis; all the joints were extremely flaccid and movable. The bones of the extremities were easily felt through the soft tissues; no edema; the skin was normal. The subcutaneous fat was small in amount, soft and somewhat edematous. The muscles of the neck were thin but of normal color and consistency. The pectoral muscles and all the muscles of the back and extremities greatly atrophied. The atrophy did not affect the abdominal muscles to so great a degree. The pectoralis major was reduced to a small fascia-like band. The color of the atrophied muscles was grayish and translucent. They were more succulent and the single muscles were not easily dissected out. They seemed infiltrated with fat and fused with the surrounding connective tissue. The intercostal muscles were reduced to thin gray sheets. The abdominal muscles, though thin, had a better color than the others. The large muscle masses alongside the vertebræ

were reduced to thin bands less than 1 cm. in diameter. There seemed no change in the nerves. They were of normal size and appearance and more prominent than is usual. The thorax was misshapen. The antero-posterior diameter was greatly diminished; the cartilages and ribs passed almost backwards from the sternum, then took an accentuation of the normal curvature, giving a flat depression in the antero-lateral situation. The lower border of the thorax flared outward like the mouth of a bell. The diaphragm was of normal color, thickness and consistency. It seemed rather better developed than normal.

The tongue, pharynx, larynx, and trachea were normal; the tonsils and lymphoid tissue of the tongue and pharynx of a development corresponding to age. All the lymph-nodes of the body were prominent. The thyroid gland was small but of normal appearance. The thymus was large, of normal color and consistency. It projected 8 cm. below the sternal notch and weighed 29.2 gm. The heart weighed 36 gm., and in all respects was normal. The aorta and other large vessels were normal with the exception of the left femoral, in which there was an occluding, fresh thrombus just below the origin of the profunda.

The entire upper lobe of the left lung and the upper posterior portion of the lower lobe were completely atelectatic and dark red in color. Nearly the entire upper lobe of the right lung was in same condition. There was no evident pneumonic consolidation, but all portions of the atelectatic lung sank in water. In the bronchi there was a small amount of muco-pus. The lower lobes of both lungs were normal; pleura normal; all the abdominal organs normal, as also were the brain and spinal cord on naked eye examination.

*Diagnosis.*—Anatomical diagnosis at autopsy, atrophy and degeneration of muscles, deformity of thorax, atelectasis of lungs, hypertrophy of thymus, fresh thrombus of femoral artery.

HISTOPATHOLOGY

*The Muscles.*—Portions of the various muscles were hardened in Zenker's fluid, liquor formaldehydi (formalin) and in Orth's fluid, sectioned in paraffin, and stained in methylene blue and eosin, in phosphotungstic hematoxylin and by the methods of Marchi and Weigert-Pal. All of the muscles affected showed the same changes though in a varying degree.

Cross section, hematoxylin and eosin: Section through some of the most altered muscles of the leg, with low power, shows the fibers arranged in well ordered fasciculi. The amount of connective tissue is increased. With low power, two well-defined masses of tissue can be seen. There are fibers which present the usual appearance of normal adult muscle. There are also masses of what seem to be accumulations of cells which are also arranged in fasciculi, but the masses are very much smaller than are the masses of normal muscles. Similar aggregations of cells are seen often at the periphery of a single muscle fasciculus. Occasionally, in the middle of the masses of small cells, single muscle fibers of the average size can be made out. At various places there are sections that appear to be the muscle spindles, that is, several muscle fibers enclosed in a definite capsule of connective tissue. The muscle fibers in the spindle vary greatly in size and the nuclei often show a central position.

Under the immersion, the larger fibers for the most part appear to be normal. Occasionally, the nuclei are found in the center of the fiber. What appeared

under the low power as masses of small cells are seen to be composed of very small muscle fibers. Although most of these fine fibers are arranged in fasciculi, they are also found in the midst of the larger fibers and surrounding the groups of these. In the large fibers there is considerable variation in size, and they are usually round or oval. Many of the large fibers are vacuolated, containing either a single large vacuole, or several small ones. Some of these vacuoles contain a small amount of finely granular material. The largest fibers in this muscle are almost invariably definitely round. Occasionally, especially at the periphery of the muscular mass, fasciculi are found which seem to be midway between the larger muscle masses and the small fibers, but in general there is a sharp distinction between the two. With phosphotungstic hematoxylin there is a great variation in the muscle stain, some of the fibers being very much darker than others. The muscle fibrillæ are not well stained. In the fine fibers the fibrillæ are rather more prominent at the periphery of the fibers. On the longitudinal section of the muscles tissue, taken from about the same region, the same arrangement of the fibers can be distinguished. The cross and longitudinal striation is apparent in both sets of fibers, but more strongly marked in the larger fibers. The nuclei in the small muscle masses seem to be extremely numerous. They are of about the same size as in the larger fibers. Many of the fibrils are so small that when the section passes through a nucleus this occupies the whole extent of the fiber. The apparently great number of nuclei is due to the number of the fibers. When a single fiber is followed along, the nuclei are not more closely set than they are in the large fibers. The cross striations in a number of measurements are nearly the same distance apart in both the large and fine fibers. The length of the fine fibers could not be easily determined either by section or by teasing. They are never so definitely parallel to one another as in the large fibers. The masses of the large fibrils in longitudinal section are perfectly straight; the masses of the smaller fibrils present a wavy appearance as though they had not contracted at the same rate as the larger fibers. Most of the small fibers are solid and they do not present the appearance of embryonic fibers. Occasionally, however, fibers are seen which are hollow with fibrillæ at the periphery presenting much the appearance of embryonic fibers, and a fiber solid throughout most of its course may present an area where it has hollowed out. They also occasionally present swellings along their course, but as a general thing they preserve the same diameter.

*Size of the fibers.*—Measurements were made of groups of the larger fibrils, taking those of both the largest and smallest diameter. The average diameter obtained by taking the longest and shortest diameters in a group of fifteen adjoining fibers is 19.2 microns. The largest fiber found in the interior of the group is 35 microns. The average diameter of another group of fibers is somewhat more, 23.75 microns. In a small group of 22 fibers, there is a variation in the sizes of the fibers which belonged to the class of large fibers of from 8 to 20 microns. The average diameter of a group of twenty-seven of the small fibers, only one diameter being necessary on account of the prevalent round shape, is 3 microns with a variation of from 1.5 to 3.5. In the longitudinal sections, fibers are found from 1.5 to 4 microns in diameter. On comparing the cross striations, taking two adjoining fibers of the large and small group, there is a difference in the distance between Krause's lines, this being from 1.8 microns to 2 microns

in the large fiber and 2.4 microns in the small, this being evidently due to a difference in the degree of contraction. This difference did not always hold, but a number of careful measurements showed in other places slight differences in the distance between the lines. Here and there among the small fibers in the longitudinal sections, single fibers are seen which show neither longitudinal nor cross striation. In these fibers there are here and there sarcous elements in the shape of double dots and occasionally rows of a half dozen or more of such dots separated by the usual interval between Krause's lines. Comparison of these fibers with the fibers of the diaphragm show that the average of the diameter of the diaphragm fibers is the same as the large fibers in the affected muscle. A study of the muscle by the Marchi method shows changes more marked in the large fibers. There is no general fatty degeneration. Single very small fat drops were commonly present, and in certain fibers there was a large amount of fat. The largest amount of fat was found in the otherwise unaltered muscle of the diaphragm. In the small fibers it was exceptional that any fat whatever was found. A study of the connective tissue in the muscle showed that this was relatively increased, but it is uncertain whether there is an actual increase in this tissue. There is no evidence at any point of any active cellular changes in the muscle. There are no phagocytic cells and no foci of lymphoid cell infiltration. The blood vessels in the muscle are normal, but of small size. The vascularity seemed small, relative to the amount of tissue.

An attempt at comparison of the size of the muscles here with those of children of the same age led to nothing of importance owing to the extreme variation in the size of the muscles in varying conditions of nutrition. Thus in a greatly emaciated child of six months, the average size from the measurement of 112 fibers of the Sartorius muscle was 5.1 microns. Measurement of the palatal muscles of a well nourishel infant at birth gave an average diameter of 17 microns; and the muscles of the larynx in a premature infant of seven months an average of 9 microns. We cannot definitely decide whether the size of the large fibers in this case varies from the normal, but probably it does not.

*The nervous system.*—Numerous sections made of the cortex, the cerebellum, the pons and medulla, and stained by the usual methods, showed in all respects a normal tissue. Sections of the cord at various levels, show very slight evidences of change. There seems no diminution in the number of cells in the anterior columns. The amount and distribution of the neuroglia is normal. The Marchi stains show very slight degeneration of the myelin in the posterior columns. The degree, however, was so slight that in the routine examination of the cord it would probably have been unnoticed. The same applies to the anterior and posterior nerve roots, and to the spinal ganglia. In the Nissl stains of the cord, no certain evidence of cell degeneration can be made out. Sections were made of the sciatic nerve at various levels which were stained by the Marchi and Weigert methods and with hematoxylin and eosin. Here and there the sections stained by the Marchi and Weigert methods show very slight irregularity in the myelin. In single fibers there is a slight stain with the Marchi. There are no cellular changes in the nerve whatever. The examination of the nerves in the muscles show more marked changes. There are nerve bundles which are in all

respects normal. The number of nerves, taking the whole mass of muscle, seems to be diminished, and among the fasciculi of small fibers, nerves are found which show evident degeneration and loss of myelin. A careful examination by the Weigert method leaves little doubt of the diminution of nerves in the changed muscle, that is, relative to the number of fibers. In these muscle fibers, no evidence is found of the terminal distribution of nerves to the single fibers. More or less definite nerve endings were found, however, among the fibers of normal size. Various branches of the sympathetic nerves which were found on the examination of the viscera, and branches of the pneumogastric nerves, were completely normal.

Sections of the atelectatic upper lobes of the lungs show congestion, atelectasis, edema, with small foci of bronchopneumonia. In the exudation here, a few diplococci conforming in morphology to pneumococci are found.

The myocardium is normal. An examination of the thrombus in the femoral artery shows this to have the usual composition of an acute thrombus, being made up of blood plates, fibrin, red corpuscles, and leukocytes. There was no examination of the blood made during life, but that within the vessels after death appears normal in the character and relative numbers of its cells.

The bone marrow of the femur shows a normal, active marrow.

It is very much regretted that there was no examination of the thymus. In the numerous pieces of tissue taken for examination, this was in some way lost. The numerous sections of the lymph-nodes show these to be normal with the exception of the almost complete absence of the germinal centers. The spleen is hyperemic, the follicles prominent, and in the germinal centers of these, almost without exception, there was extensive necrosis of a type exactly resembling that so commonly found in diphtheria. Microscopic examination of the liver, pancreas, adrenal, kidneys, intestinal canal and thyroid shows these organs to be normal. In the thyroid there is the usual amount of colloid.

## ABSTRACTS OF CASES FROM THE LITERATURE

In view of the rarity and the interest of this disease, it seems worth while to give short abstracts of the cases hitherto reported.

MUGGIA.[2] Female child, family history negative. Pregnancy and birth normal. Directly after birth the child seemed normal. It cried, passed meconium, nursed and urinated. After a few days it was noticed that the child moved neither the arms nor legs. On observation, nutrition, size, weight and organs were normal. The limbs showed an absolute lax paralysis. The sensation of skin was normal. The superficial reflexes and the patellar reflexes were normal, but weakened. The electrical reaction of both nerves and muscles was not diminished. After four months' observation, there was no change in the condition and child continued to develop normally.

BATTEN.[3] These three cases reported by Batten, the first case following Oppenheim's articles, are properly considered by Collier and Wilson to belong to the group:

CASE 1.—Male, age about 6 years; the third of four healthy children; never stood; could sit up but not kneel; was intelligent; on examination was thin and

small; could get into sitting position; progressed by rolling over and over; no localized atrophy or hypertrophy; all movements could be performed with arms; unable to extend legs or to flex legs on abdomen; extensors and flexors of foot were fairly good; abdominal and dorsal muscles were weak. Contraction could be obtained in most muscles on strong stimulation, but not in quadriceps or gluteal.

CASE 2.—Male, age 7, small at birth, legs always contracted; never able to walk. On examination limbs were thin and wasted; long hands and feet; face somewhat expressionless, eyes prominent, facial muscles act; unable to walk; arms thin and wasted; muscles small; all movements could be performed; legs thin; knees could not be straightened owing to contraction of ham strings. Most movements could be performed, but legs could not be extended; knee-jerks absent; all muscles reacted to a moderately strong faradic current.

CASE 3.—Female, aged 6; could not stand or sit up, but could remain in sitting position; could always move both legs and could pick up small things with either hand; was intelligent. On examination, small for age, eyes prominent, sat up if placed, or lay on back with knees flexed; feet and hands appeared long; knee- and hip-joints could not be fully extended; muscular wasting general; muscular sense normal, knee-jerk and plantar reflex absent.

SCHULLER.[4] He demonstrated a child, male, age 19 months. The child was weak from birth. It learned to sit up and stand. After ten months, it was no longer able to stand nor to sit upright. On examination in addition to slight symptoms of rickets, there was a high degree of hypotonia of the muscles of the lower extremities, but without evidence of atrophy. There was absence of the deep reflexes; diminished electric excitability; active movements of legs could be carried out in but slight degree.

SPILLER.[5] Male, aged 22 months. The condition was first noted at five months; has never been able to hold anything in hand; at entrance into hospital child was well developed for 20 months old; muscles not wasted, but soft and flabby. The limbs were moved voluntarily at all joints, but the movements were very weak. There was a remarkable range of passive movements of legs, the feet could be placed behind the head while the front of thigh was in close contact with the trunk. There were no patellar or tendon reflexes; irritation by pin caused motion. The child had been constipated since 2 months old, which was attributed to weakness of the abdominal walls. The muscles reacted to the faradic current. Autopsy: No rigor mortis; muscles flabby. On cutting into calf muscles a great deal of subcutaneous fat and little pale muscle tissue were found; in sole of foot muscle almost absent. Microscopically the muscle fibers were small and those from the foot smaller than those from the back. The transverse striation was normal, the longitudinal not so well marked. The brain, spinal cord, and nerves were normal; no degeneration by Marchi stain. Spiller regards an arrest of development of the muscles the essential pathologic condition. Smith gives a subsequent report on the examination of the thymus.

OPPENHEIM.[6] Child (sex not stated), aged 1 year and 7 months; no hereditary trouble; soon after birth it was noticed that the child could not move its extremities though all the muscles supplied by the cranial nerves were normal.

When 9 months old some movement of the arms was obtained, but the legs remained completely lame. The child was well developed and nourished. There was slight reduction in the volume of the muscles, which had a peculiar doughy feeling. There was diminution in the muscular tonus; the tendon reflexes in the legs were abolished, and the muscles did not respond to mechanical or electrical stimulation, with the exception of some feeble contractions in the peroneus.

BERTI.[7] CASE 1.—Boy, 3 days old. Two days after birth it was noticed that with the exception of the eyes, lips, tongue, and head, there was no motion. He lay with stretched limbs, crying weakly. The breathing was shallow and frequent, of diaphragmatic character. All the muscles of the extremities and the trunk with the exception of the diaphragm seemed to have no function. There was complete atony of the muscles. After three weeks the respiration was deeper. On stimulation there was slight motion of one arm. Subsequent history unknown.

CASE 2.—Girl, 5½ years old. On the day after birth it was noticed that the child, otherwise normal, seemed to show no life in the body with the exception of the head. After three weeks there was slight motion in one arm and in some of the fingers. After a year and a half the child could lift up the arms and there was slight movement in the legs. This condition lasted until 5½ years old, the child becoming emaciated. Now all movements are carried out slowly. She stands with legs spread out. The muscles are soft and relaxed. The electrical stimulation is diminished; knee-jerks sometimes doubtful; easily exhausted; no alteration in sensation, no sphincter trouble.

KUNDT.[8] Child, 18 months old. No hereditary trouble; two other children are normal; the pregnancy and birth were normal. The fetal movements were felt just as in the other pregnancies; mother noticed no movements of feet from the first; after six months there were movements of feet and lower limbs; thighs remained motionless; child could sit up, but could not stand. The arms were normal. The child was well nourished; subcutaneous fat abundant; the muscles were extremely lax on palpation. All passive movements of the hip joints easily carried out, but some opposition to extension of lower leg. The knee-jerk was absent. The Achilles reflex appeared on the left, but was imperfect on the right. Electrical stimulation produced contraction of the lower legs. After three months' observation a slight improvement was noticed. There was never reaction of degeneration.

ROSENBERG.[9] Male, 2½ years old. Family history negative. Mother did not feel fetal movements during pregnancy. Pregnancy and birth normal. Child nourished by bottle. The arms, head, face, and eyes moved normally. The child sat up at seven months. At eleven months on attempting to stand there was no strength in knees or hips. Child at time of report could not stand or walk. In other respects it was normal. The upper and lower legs could not be moved. The feet and toes could be actively moved. When a leg was lifted it fell as a dead weight. Contractions in the apparently paralyzed muscles were produced by pain. The legs showed no atrophy. There was entire absence of muscle tone and very extended passive motion could be made. The feet could be brought in contact with the ears. Palpation showed a decided difference between the affected and the normal muscles, the former having a soft doughy feeling. There was

absence of knee and Achilles reflexes. There was complete absence of electrical reactions in the gluteal, in the quadriceps and in the adductors. In the lower leg only the peroneous gave a reaction. After six weeks' faradic treatment some improvement was noted.

Iovane.[10] Male, aged 3 months. Family history negative, normal pregnancy and delivery. Child appeared healthy and took the breast. On the first day it was noticed that there was no voluntary movement of the arms or legs and that the head rolled about on the trunk. When seen at three months, there was flaccid paralysis with absolute atony of muscles of arms and legs; feeble movement at wrist; muscles of trunk atonic, only abdominal reflexes present; slight response to faradic current, none to galvanic. Child died at five months with bronchopneumonia.

Sorgenta.[11] Both children by the same mother. No movements during pregnancy. In both clinical history about the same. Both well developed at birth and from birth unable to move arms or legs; absence of cutaneous and deep reflexes; no reaction in muscles of legs; weak in arms. Death in one on fortieth day, in other on fifteenth day. In both cases convulsions preceded death. No autopsy.

These cases of Sorgenta have been excluded by Collier and Wilson, chiefly in view of its familial type and classed with the myopathies.

Comby.[12] Male, aged 8 years. When seen first in September, 1905, could neither walk nor stand; kyphosis on sitting; intelligence good. The only defect was in the muscles, which were soft, but not atrophic; could move legs but they were not strong enough to support him.

Cattaneo.[13] Female, aged 4 months. Birth normal. Fetal movements not felt. Breast fed. After birth it was noticed that the child could not move hands or arms. Father thought it could move arms at time of report. Could not hold head up. Observation showed a well nourished child; only slight movements of hands and feet; cutaneous and deep reflexes absent; electrical reactions diminished.

Bing.[14] Male, 3½ years old. A typical case. It was at once noted that the legs were passive appendages to the body and could be moved readily in all directions. A normal birth. Congenital bilateral pes varus. Great weakness of muscles since birth. Child could neither stand nor walk. Arms could be moved, but movements weak. Head could be held but a short time in one position. Knee-jerks absent, no disturbance of sensation or of sphincters. Bing removed a piece of muscle but does not state from which part and found it normal, although there might have been some question whether the nuclei were not more abundant than normal. He questions whether the condition is to be regarded as functional or due to a non-development of the spinal cerebellar tract which governs the tonus.

Tobler.[15] Male child, the first born. First observed at 20 months and under observation three years. Fed on breast for six months. From the first the loss of motion was striking. Examination at 20 months showed a well nourished child. All extremities in condition of complete atony but no paralysis; some motion in arms but slow and weak. Atony even extended to facial muscles, but the move-

ments of tongue and eyes were normal; electrical stimulation greatly diminished and in part lost; sensation not affected; intelligence good; no change during continued observation for three years. Death probably from diphtheria at 5 years. No observation as to fetal movements.

VARIA AND DEVILLERS.[16] First child; fifty-nine days before birth mother fell and was laid up with periostitis until eight days before birth. During pregnancy, both before and after the accident, fetal movements were felt; child under observation for nine months; female child; arms and legs immobile; all the muscles abnormally flaccid. The head rolled about indifferently when not supported. There was spinal kyphosis when child was seated, which disappeared on lying down. Death from bronchopneumonia when 9 months old. (Pieces of muscle and cord were sent to Dejerine for examination but no report has been published.)

COMBY.[17] Male, aged 4 months. When one month old the child had an attack of diarrhea and it was then noticed that the muscles were paralyzed. When examined, legs immovable; no muscular wasting; knee-jerks absent; no support for head; electrical reaction showed hypo-excitability of right leg; no reaction of degeneration. After a year muscular atony persisted.

CARY COOMBS.[18] Female, aged 10. Flabbiness of one hand noticed one-half hour after birth. Nothing further was noticed until time to walk. Then it was found that the legs would not support her; could not walk by herself until 2 years old; arms most affected; ankles often turned causing her to fall; extraordinary flaccidity of all joints; knuckles could be made to touch the back of the wrist; lower limbs very hypotonic, but not so much so as upper; knee-jerks and tendon reflexes were present; electrical excitability was diminished. Muscles could be distinctly felt, but they were small, soft and doughy.

LECLERC.[19] Female, aged 4 years. Mother felt fetal movements as in the case of her other children. For the first days the child appeared normal. A bronchopneumonia developed at 6 weeks of age and after this the paralysis was observed. The child then appeared completely paralyzed, incapable of making any movements of extremities. Head falls on shoulders when moved. From this time a slow but progressive improvement took place. At the time of the report the child could move the limbs, but the movements were feeble. Not a true paralysis, but muscular atony. The face and all muscles innervated by cranial nerves were normal. The passive movements of the joints were greatly exaggerated. The muscles were not atrophied, but seemed extremely soft. The intelligence was slow in developing.

BAUDOUIN.[20] Child, 4 months old, female. Pregnancy and birth normal. Since birth neck, trunk, arms, and legs were immobile. Muscles supplied by cranial nerves normal, except for slight internal strabismus of right eye; complete flaccid paralysis in trunk and limbs with the exception of feeble movements of fingers and toes; absence of deep reflexes; respiratory muscles were affected. The thorax dilated very slightly during respiration. Faradic excitability was diminished. Death from bronchopneumonia. (Baudouin says that the disease tends naturally toward recovery and if cases are met with early a complete recovery is possible, which is somewhat at variance with the results of his autopsy.)

He found in the cord at the level of the eighth cervical segment that the cells of the anterior horns were diminished in volume but there was no evidence of neuron phagocytosis. He thinks there is probably an arrest of development. Section of the anterior and posterior nerve roots showed the anterior four or five times smaller than the posterior. The posterior stained more deeply than the anterior. In the anterior root the sheaths were more widely spaced and separated by amorphous tissue. Sections of the sciatic nerve stained with Marchi showed no fragmentation of the myelin. In sections stained by Weigert's the nerve was not well stained, the myelin sheaths were thickened and not equal in number in the different bundles. He concluded that with the myelinated fibers there were numbers of nerves not yet myelinated. The same lesions were found in the crural, cervical and median nerves. The condition in the nerves was not a neuritis but an arrest of development and a retardation of myelin formation.

The muscles presented very profound lesions, varying little according to the muscle examined. The connective tissue sheaths were numerous and thickened. The vessels were normal, but often surrounded by young cells. The muscular fibers were much changed. There were masses of small fibers from 6 to 8 microns in diameter and along with these very large fibers often reaching a hundred microns. The nuclei were increased in number and often lay in the interior of the fibers. The striations were normal and there was no degeneration. The diaphragm was the least affected. The skin was normal, the lungs showed disseminated bronchopneumonia. There was slight sclerosis of spleen with follicles more accentuated than normal. The thyroid gland was sclerosed and contained no colloid. There was sclerosis of the thymus with small Hassall's corpuscles. The condition was due to some cause which had suspended the development of the marrow and the nerves, and through these changes the muscle had become affected.

AUSSET.[21] Female child, 2 years, 9 months old. Mother had five children, two born dead. No fetal movements during pregnancy. After birth the mother noticed that the child was unlike others. It was inert and lay five or six hours without demanding the breast; did not move limbs even when crying; there was slight movement of arms. At 18 months there was some febrile disturbance and at two years whooping-cough. On observation, nutrition appeared good; fat abundant on lower legs; slight movement of arms; legs immovable; no actual paralysis; when leg was lifted it did not drop as rapidly as would a paralyzed leg. The joints were not abnormally movable. The left leg was smaller than the right. The electrical reactions were normal.

BRUNARD.[22] Child aged 2 years. External appearance was that of a well nourished infant rather deficient in fat. No hereditary trouble. Birth normal; fetal movements felt; breast nutrition. At the age of 2 months there were convulsions which had not reappeared. The first teeth were late in appearance. The attitude was striking. The child lay on her back, the legs flexed on the thighs, with total abduction. The extremities could be moved, but the child could not take hold of an object; could not walk; gave picture of child sitting down, the body bent forward, the face on the ground between the feet. The patellar reflex was absent; electrical reactions did not appear to be diminished; no trouble with

respiration, circulation or digestion. The child was idiotic. (In this last the case departs from the type, since all the other cases showed normal intelligence.)

COLLIER AND WILSON.[28] CASE 1.—Boy aged 4. Normal pregnancy and birth. No mention of fetal movements. At birth well-shaped but thin; breast fed. The position assumed naturally from birth was one of flexure of hip and knee and extreme dorsiflexion of ankle; legs and arms weak and limp; could not hold head erect. On examination, a small, thin, soft, limp child; muscles small and absolutely atonic, the joints so relaxed that the limbs could be placed into all sorts of fantastic positions without discomfort. The muscles have a soft, velvety feel. A limb held up by its proximal end can be shaken like a flail. There was contraction of the iliopsoas, adductors, and ham strings on both sides. With this restriction, all voluntary movements could be performed quickly and with normal range, but the power was very feeble. The vertebral column bowed in the sitting posture but the curve disappeared when the child was held by the shoulders. The soles of the feet were almost flat, soft and like long pads. Faradic and galvanic excitability was lowered. The deep reflexion without exception were absent.

CASE 2.—Boy, aged 7. The mother was weak in the limbs when a child, and several members of her family could not close the eyes properly. Birth normal. No mention of fetal movements. Soon after birth it was noticed that the child was unnaturally limp and could not hold up his head; had never been able to walk; slow improvement since three years old. On examination, head large, facial muscles weak, inability to close eyes properly; universal flaccidity and weakness; the muscles were soft and weak; impossible to differentiate muscle from adjoining tissue by palpation. All muscles contracted voluntarily, but too feebly to do any useful act. All reacted to faradic current. Child had a peculiar triangular face and open mouth which may have been due to maldevelopment or to muscular contraction preventing the full growth of the mandible. The superficial reflexes were normal, the deep entirely absent. There had been gradual improvement and when last examined the child could walk a little without support.

CASE 3.—Boy, aged 5½ years. Family history negative. Child breast fed. Nothing noticed for six months with the exception that the child placed his limbs in extraordinary positions. After this the mother noticed that the legs were weak. He finally was able to stand when holding on to something; then became weaker and weaker in the legs. On examination, a pale, thin child, of average height; intelligence good; no difficulty in speaking and swallowing. Muscles of upper extremities were small but all voluntary movements could be performed. There was absolute hypotonia of all the muscles, with relaxation of the ligaments and flail-like joints. Muscles of the neck and trunk were thin and weak. He could raise his head only when lying in the supine position and sat up with difficulty. In the lower extremities there was slight contraction of the flexors of the thighs and decided contracture of the muscles of the feet. The faradic excitability of the muscles was diminished. The superficial reflexes were normal; the deep, entirely absent. Continued improvement occurred.

CASE 4.—Girl, aged 1 year, 8 months. Family history negative; pregnancy and birth normal; fetal movements felt; breast fed; child normal until 12 months old. At this time she was ill for a month with an attack of bronchitis. At end of illness it was noticed that she could not move her legs; arms not affected. On examination, a thin but otherwise fairly developed child; motion of upper extremities normal, but weak and flaccid; the muscles of the lower extremities were absolutely atonic; movements very weak; considerable voluntary control; a flail-like condition of the joints; the deep reflexes were absent; the faradic excitability was diminished. After being at the hospital for three months marked improvement in the power of all muscles was noticeable. (The cases of Collier and Wilson are rather different from the other cases which have been reported, in the age of the patients, in the slighter degree of the muscular involvement, and the time after birth of the development of the condition.)

GASTONGUAY.[24] Child aged 3 years and 8 months. Mother perceived no fetal movements; nothing abnormal noticed for six weeks; then after a pulmonary attack the child appeared completely paralyzed with the exception of the face and pharynx. Child nursed and drank perfectly. When seen there was no complete paralysis, but atony of the muscles. This atony extended to the ligaments, rendering the joints much more flaccid and giving greatly exaggerated passive motion. The muscles did not seem atrophied but were much softer than normal. All muscles enervated by the cranial nerves were intact. The skin was not very supple, that of the lower extremities showed a hard, smooth edema. The mental development was retarded. Slight improvement occurred while under observation.

LEREBOULLET AND BAUDOUIN.[25] Child, aged 11 months. Flaccid paralysis having its maximum in the muscles of the neck. Head rolled unsupported. The extremities were equally affected; reflexes diminished but not abolished. Death, with fever and dyspnea, due to a beginning pulmonary septicemia. Convulsions were seen and during these the flaccidity gave place to contraction. Autopsy: The cord and brain were examined by methods of Nissl and Marchi. These were found normal. No diminution in size or number of the cells in the anterior horns. The muscle lesions were marked, particularly in the neck muscles. The fibers were of irregular size. The transverse striations were absent; the longitudinal present; a considerable increase in nuclei.

LAFFER.[26] Girl, aged 8 years. Birth normal. Soon after birth, it was noticed that the face was immobile; could hold head erect when a few months old, and sit up when 7 months; began to walk when 14 months old, but with a peculiar waddling gait. There had been slight improvement since. There was great flaccidity of joints, particularly those of the lower extremities, and muscular weakness. (This case offers differences from the other cases in the first appearance of the condition in the face. There was no note of flaccid atony in the lower extremities until she began to walk at the age of 14 months.)

ROTHMANN.[27] The first child of the mother. The mother fell on her back in the eighth month of pregnancy. Fetal movements were felt but were weak. When 14 days old the mother observed that it did not move the limbs, and thought the condition was present from birth. The child when seen at 4 months

was a typical case. A badly nourished child of normal size. Skull, otherwise normal, showed closure of the large fontanel. The legs were relaxed and showed no trace of active motion. On the upper and lower legs the skin was thick, the fat abundant; the muscles could not be palpated. The legs could be moved in any direction without opposition. The skin and tendon reflexes of the legs were absent. The arms could not be actively moved. There was movement of the fingers. The head fell to one side or forward or back on the body when moved. The face, the pharynx, the tongue, the eyes, all moved normally. There was no paralysis of the sphincters. Electric stimulation procured effect only on flexors of arms. When crying the expression was normal.

*Autopsy.* The thymus was large for the age of 5 months. The cord was small and firm. Microscopically the cord showed extensive disappearance of the large motor ganglion cells of the anterior columns. The few motor cells which were retained were smaller than normal and showed evidences of degeneration. The absence of all fresh degeneration showed that the condition must have lasted several months. There was also a diminution of cells in Clark's columns. The white matter was entirely normal. In the vicinity of the hypoglossal nucleus there was chromatolysis and apparent beginning of the process. The investigation of the peripheral nerves of the arm and leg showed diminution in the size of the fibers, with thickening of the perineural connective tissue septa. There was no degeneration. The nerve fibers in the muscle were made out by the gold chlorid method; the end plates were not seen. Since according to the condition of the anterior horn cells only few motor fibers could be present, they must either have vanished without leaving a trace, or there must have been a regeneration in fetal life. The biceps showed increase of the connective tissue with increase of nuclei. In the quadriceps there was infiltration of fat between the fibers with small-cell infiltration. The intercostal muscles were normal. The thymus showed an increase in the Hassall bodies and thickening of the walls of the vessels.

Collier and Holmes.[28] Child, aged 3½ years. Pregnancy and birth normal. No mention of fetal movements. Mother noticed that the child did not kick like other children, but no other peculiarity was noted until a year old, when she tried to stand him up and found that his legs doubled up under him; was never able to stand or to walk; could not himself assume a sitting position. The diaphragm and intercostals acted well. There was no local muscular wasting. Passive movements at all the joints was free, and flail-like movements of hands and fingers could be produced by shaking. In the lower extremities hypotonicity of muscles of thigh and calf. The feet could be easily touched together behind the head. Deep reflexes absent; superficial, normal. From this patient a piece of thigh muscle was taken for examination, as well as from one of the previous patients of Dr. Collier, who had died from bronchopneumonia. No mention is made of the examination of other tissues and there is no general account of the autopsy. The muscles were fixed in Zenker's and sections made. The muscles appeared very pale and infiltrated with fat. Very few spindles could be found in the more severely affected muscles. The majority of fibers were much reduced in size, and showed an average diameter not exceeding twelve microns on cross section; they were irregular in shape, the cross striation well preserved. The

nuclei seemed to be largely in excess of the normal. A small number of fibers were enormously enlarged, up to 150 microns. Regressive changes were present in many of the hypertrophied fibers. There was great increase of connective tissue in the affected muscles. The muscle bundles were normal. The intermuscular nerve fibers were small. The muscle changes are the essential pathologic lesions. They may be regarded either as due to regressive changes in previously normal fibers, or as due to defective development. He gives photographs of the slides which show an almost identical condition with that seen by us, with the exception of the size of the fibers, that of the atrophic fibers being 12 microns. The autopsy description was limited to the muscles.

J. P. Crozer Griffith.[39] At a meeting of the Philadelphia Pediatric Society Griffith showed a typical case in a boy about 17 months.

Ashby.[40] Girl aged 8 years. Condition existing from birth. The patient lay in bed as if completely paralyzed. All muscles of the body, including face, were flabby and wasted; difficulty in masticating solid food; reflexes feeble; electrical reactions normal; all special senses normal. The condition gradually improved. (This case departs from the usual type in the involvement of the facial muscles and those of mastication.)[41]

## SYMPTOMATOLOGY

The description of the disease first given by Oppenheim covers very well the main points in the symptomatology. All reports agree as to the flaccid paralysis, most marked in the lower extremities, and the general non-involvement of the muscles supplied by the cranial nerves. The only possible exceptions are a difficulty in deglutition in two cases, and in one an inability to close the eyes. The great flaccidity of the joints, which might be supposed from the condition of the muscles, is also generally described. No description of this can be better than that given by the mother of one of Collier's patients: "By whatever part of the body I held him up, all the rest of him hung down like so many pieces of yarn." When we consider the remaining symptomatology there is much uncertainty. Sensation in the affected parts seems on the whole to be unimpaired, but an abnormal tolerance of strong faradic currents has been mentioned. The reflexes may or may not be present. Contractility is generally produced by the faradic current, and there is absence of the reaction of degeneration.

## ETIOLOGY

There is no accurate knowledge of the onset of the disease, whether sudden or gradual. In all the descriptions it has been impossible to give any exact time so that the onset must have been gradual; possibly weakness preceding atony, and a gradual extension of the field; in some of the

descriptions this is evident. Oppenheim and those following have laid weight on the congenital nature of the disease as being one of the important conditions belonging to it. Certainly this is involved in much doubt. It is true we know nothing of the time a muscle degeneration may be in progress before symptoms are produced, but if we assume that the beginning of the disease is coincident with the appearance of the flaccid paralysis, then it certainly is not usually congenital. Of all the cases, in but five it is stated that it was present at birth. An important point bearing on its congenital nature is that of the fetal movements of the child. The degree to which this is felt varies and its absence does not denote fetal paralysis. In the cases we have collected, the presence or absence of fetal movements is mentioned in ten. In these the fetal movements were felt in seven and were absent in three. The usual statements of the time after birth are vague. The time extends in one case to seven months, in another ten, in another twelve, and in one case seven years. In regard to the frequent cases in which the condition was noted from two to thirty days after birth, it does not seem probable that it could have been present from birth and escape the attention of the mother, the nurse and the physician. We have asked several obstetricians with regard to this and they have not thought it possible. The mothers who have been asked have with some heat denied the possibility, and have even regarded the question as an attempt to secure antisuffrage evidence by showing in the female gross deficiency in the powers of observation. In none of the cases has it appeared in connection with an acute infection. In four cases it is stated that it appeared after a bronchopneumonia, and after diarrhea in one. In view of the frequency of these conditions, there is evidently no relation. It is scarcely possible by symptomatology alone to make a disease entity. To that belongs first a proved etiologic factor, or in the absence of this, definite pathologic lesions.

### PATHOLOGY

There have been six autopsies made on cases and in two additional cases examination of the muscles, and there is much disagreement as to the character of the lesions. In one of the autopsies by Baudouin there was diminution in number and degeneration of the anterior horn cells and absence of myelination in the nerves; in another, the case of Lereboulet and Baudouin, the cord and nerves were normal. In Rothmann's case there was marked involvement of the anterior horns and the nerves.

In Spiller's case, in ours, and in one of Baudouin's, the cord was normal. Presumably it was also normal in Holmes' case, since he makes no mention of its examination.

There is much more unanimity in regard to the condition in the muscles. Spiller regarded this as due to imperfect development, and most descriptions mention the great diminution in size of certain fibers and the great enlargement of others. Holmes found fibers up to 150 microns in diameter, and Baudouin found fibers of 100 microns. The photograph which Holmes gives of a cross section of muscle certainly shows no such fibers and might have been made from a section of the muscle in our case. Bing found the muscle normal, though there might have been some question of a nuclear increase. Such variation in the anatomic lesions are akin to the variations in the symptomatology and are not sufficient to serve as a basis for the creation of a disease entity. Even in the case of the lesions in the muscles, there are a number of conditions which produce similar lesions, as the great atrophy of certain fibers with a normal condition, or an enlargement of others.

The condition of the thymus gland is interesting. It was found to be enlarged in Spiller's, Baudouin's, Rothmann's and our case. Whether there is any relation between the thymus and the condition is uncertain. We regret that no microscopic examination of the gland was made in our case. Spiller and Smith[81] found fibrosis, enlargement of the Hassall bodies, endothelial proliferation, and arteriosclerosis. Baudouin found sclerosis with diminution in the Hassall bodies, and Rothman enlargement of the bodies with thickening of the walls of the blood-vessels. To any one who has made many examinations of the thymus, these statements do not convey anything. There is no organ in the body which varies so enormously in size as does the thymus in children under one year. We have taken from the records of the pathologic laboratory, Harvard Medical School, the weight of the thymus in sixty autopsies on children under 1 year of age and found a variation from 1 to 26.5 gm. The average is 4.5 gm. There is no record of weight equal to that of the thymus in this case, the next highest being 26.5 gm. in a child of four months with status lymphaticus.

There is no reason to believe that the disease is an infectious one. The onset, the distribution of the lesions, and the absence in our case of any changes which might show a past infection even, all speak against

this. The lesions are not focal. Neither single muscles nor single muscle groups are affected. All the muscles innervated by the spinal nerves are affected though in different degree. The disease has further never been seen in an epidemic or in an endemic form. The reported cases are generally distributed and have become more numerous in late years because attention has been more attracted to the disease.

It seems much more evident that the disease is toxic rather than infectious and that in certain cases, at least, the action of the toxic agent is either directly on the muscle fibers or on the terminal nerves or nerve endings. It also seems probable that such a toxin is produced not in the infant but in the mother. There does not seem to be any relation between the disease and any other disturbance in the child, no relation to food or digestive disturbances. Some of the children were fed on the breast, others on the bottle; generally the children were healthy at birth. It is perfectly possible to conceive of the presence of a toxin in the blood of the mother from the action of which she would be protected by the presence of antibodies. The toxic agent would be transmitted along with the protecting antibodies through the placental circulation. After the birth of the child the action of the toxin would not be counteracted by the antibodies which are no longer received from the mother. We can conceive of such a toxin acting either on the spinal cells or on the nerves or on the muscles, or on all three tissues, of its being constantly present in the mother's blood, which would be the case in the Werding-Hoffman[22] familial type, or only temporarily present as in the cases of myatonia. It is, of course, difficult to explain under such an hypothesis why single muscle fasciculi and single fibers in a fasciculus should remain normal as in our case.

## PROGNOSIS

The prognosis in these cases is doubtful. Without actual destruction of nerve cells there should be considerable capacity for regeneration, and improvement has been seen in many of the cases. We do not know, however, whether muscles so altered as these are capable of complete regeneration. The few reports of cases up to 10 years of age do not seem to give a very good prognosis. Of course much will depend on the extent of the lesions.

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BIBLIOGRAPHY

1. Oppenheim: Ueber allgemeine und localisierte Atonie der Muskulatur (Myatonie) im frühen Kindesalter, Monatschr. f. Psychiat. u. Neurol., 1900, viii, 232.

2. Muggia: Un caso di paralisi completa congenita dei quartto arte, Pediat. Napoli, March, 1903.

3. Batten: Three Cases of Myopathy, Infantile Type, Brain, 1903, p. 147.

4. Schuller: Wein. klin. Wchnschr., 1904, p. 722.

5. Spiller: General or Localized Hypotonia of the Muscles in Childhood, Bull. University of Penn., 1904, xvii.

6. Oppenheim: Ueber einen Fall von Myatonia congenita, Berl. klin. Wchnschr., 1904, p. 255.

7. Berti: Contribuzione all' atonia musculaire congenita di Oppenheim, Pediat. Napoli, 1905.

8. Kundt: Myatonia Congenita, Leipsic Dissertation, 1905.

9. Rosenberg: Ueber Myatonia Congenita, Ztschr. f. Nervenh., 1906, xxxi.

10. Iovane: Contributo clinico allo studio all' atonia musculaire congenita d'Oppenheim, Pediat. Napoli, March, 1906, p. 190.

11. Sorgenta: Due case di atonia musculaire congenita di Oppenheim, Pediat. Napoli, May, 1906.

12. Comby: Atonie musculaire congenitale, Arch. de méd. d. enf. Par., 1906, ix.

13. Cattaneo: Sulla paralisi dei neonati a sulla myatonia generalizzata di Oppenheim, La Clinique Mod., June, 1906.

14. Bing: Ueber atonische Zustände der kindlichen Musculatur, Med. Klin., 1907.

15. Tobler: Ueber congenitale Muskelatonie (Myatonia congenita), Jahrb. f. Kinderh., 1907, lxvi.

16. Variot and Devillers: Un cas d'atonie musculaire congenitale, Bull. Soc. de pédiat. de Paris, 1907, ix.

17. Comby: Atonie Musculaire congenitale, Bull. Soc. de pédiat. de Paris, 1907, ix.

18. Coombs, Carey: Congenital Hypotonia (Congenital Amyoplasia), Brit. Med. Jour., 1907, p. 1415.

19. Leclerc: Gaz. d. hôp., 1907.

20. Beaudouin: Amyotonia congenita, Semaine méd., 1907.

21. Ausset: Sur un case d'atonie musculaire congenita. Echo méd. du nord., 1908, xii.

22. Brunard: Un cas de myatonie congenital Maladie d'Oppenheim, La Clinic, 1908.

23. Collier and Wilson: Amyotonia Congenita, Brain, 1908.

24. Gastonguay: Un cas d'atonie musculaire congenitale, Maladie d'Oppenheim, Bull. méd. de Quebec, 1908, x.

25. Lereboulett and Beaudouin: Un cas de myatonie avec autopsie, Soc. méd. de hôp., 1909, xxvii.

26. Laffer: Myatonia congenita of Oppenheim with a report of case.

27. Rothmann: Ueber die anatomische Grundlage der Myatonia congenita, Monatschr. f. Psychiat. u. Neurol., 1909, xxv.

28. Collier and Holmes: Amyotonia Congenita, Proc. Roy. Soc. Med., Neurol. Sec., 1909, ii.

29. J. P. Crozer Griffith: Arch. Pediat., April, 1910.

30. Ashby: A Case of Congenital Myatonia, Arch. Pediat., May, 1910.

31. Smith, A. J.: Histological Changes Encountered in the Thymus and Elsewhere in a Case of Congenital Hypotonia, Bull. University of Penn., 1905, xviii,

32. Werding-Hoffman: Weiterer Beitrag zur Lehre von der hereditären progressiven spinalen Muskelatropie in Kindesalter, Deutsch. Ztschr. f. Nervenh., 1897, x.

33. An additional case is that reported by Beevor: A Case of Congenital Spinal Muscular Atrophy and a Case of Hemorrhage into the Spinal Cord at Birth Giving Similar Symptoms, Brain, 1902, xxv, 85.

# EPIDEMIOLOGIC AND ETIOLOGIC STUDIES OF ACUTE POLIOMYELITIS IN PENNSYLVANIA

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During 1907 some 200 cases of poliomyelitis developed in a district in the northwestern section of Pennsylvania, extending from 78° 55′ to 80° 15′ west longitude and from 41° to 41° 30′ north latitude. The outbreak apparently began the latter part of July in Elk County and in early August in Venango County, appearing first in Elk County at Ridgway and in Venango County at Oil City; later at Du Bois, in Clearfield County and at Eau Claire in Butler County. In this outbreak the height of the epidemic seemed to be reached the latter part of September and by the end of November the disease was practically stamped out. A small outbreak occurred in Adams County during July and August, 1908. Sporadic cases, only, occurred during 1909.

During the summer of 1910 an epidemic of considerable proportions developed in widely separated sections of the state, reaching a total of 1,076 cases before dying out in the early winter months. The 1910 epidemic began in June in the Lehigh Valley, in July in Lancaster County and in Potter County, and later small outbreaks developed in Westmoreland and Fayette Counties, with scattering cases throughout fifty-five counties. In the Lehigh Valley in the vicinity of the two Bethlehems, Allentown and Catasauqua, the outbreak assumed rather alarming proportions and the same may be said of Lancaster County. In Philadelphia the greatest number of cases occurred in a beautiful section of Germantown, in the northern part of the city, and in a new and rather open section of West Philadelphia, with well paved streets and plenty of shade.

The 1,076 cases reported during the year 1910 were grouped geographically with reference to topography, showing conclusively that

elevation played no part, as cases occurred at Philadelphia near sea level in considerable numbers and others were reported in areas fully 2,500 feet above the level of the sea. Similar charting was made with reference to distribution of surface waters, with negative results. The only features of this part of the analysis worthy of mention are that moisture and possibly open water-courses may have played some part in the distribution of the disease.

In classifying cases by geologic formation it seems to hold true that over sand and gravel formation the disease was less prevalent and that it was more prevalent in districts not so favorable for drainage. The character of the surface of the earth in each locality and of the subsoil seems to have been worthy of special note in this relation; and while it is of no distinct value in relation to our present knowledge of the disease, it may be worth recording when making future studies.

We were able to learn nothing of value in relation to the distribution of vegetation other than that the disease was most prevalent after vegetation had reached its height and during the stage when full development of plant life had been reached or passed, the greater number of cases resulting when plant life was on the decline and about the time the harvest season had ended. Possibly fungus growths favored by local death of plants may have furnished a nidus for unusual development of an intermediate host in which the virus may have passed through some stage of its life cycle.

Seasonal distribution shows that the disease is most prevalent during the height of summer and early autumn. This distribution is well shown by grouping reported cases by months of sickening, as follows:

| | Cases |
|---|---|
| January | 0 |
| February | 3 |
| March | 2 |
| April | 1 |
| May | 4 |
| June | 27 |
| July | 162 |
| August | 336 |
| September | 318 |
| October | 152 |
| November | 52 |
| December | 10 |
| Month of onset indefinite in | 9 |

During the 1907 epidemic, the chief of the laboratories spent considerable time in the infected area and secured pathologic materials for laboratory study. Full details of this work will be found in the Department's Annual Report for the year 1907. Research work begun at that time has been continued with slight interruption until the present time. It is doubtful whether monkeys inoculated at that time developed a true poliomyelitis; probably the virus secured was not fresh enough for research work. Bacteriologic studies made at that time were not productive of results.

With the beginning of the 1910 outbreak a branch laboratory was opened in Bethlehem through the cooperation of St. Luke's Hospital, and later a second branch laboratory was opened in the city of Lancaster through the courtesy of the city chemist. A great mass of data was secured, and a number of autopsies were performed. The tissues, together with a number of lumbar punctures, gave us constant material for laboratory study, and as soon as good strains of virus were secured inoculation experiments gave us the disease in considerable numbers of cases in artificially infected monkeys.

In addition to making careful studies of tissues and spinal fluids secured from the bodies of those suffering from the disease and in making careful inoculation experiments with these materials, a vast amount of work was done in studying smears of blood and of nasal mucus. Careful studies of bowel contents and urine were carried out, an offer being made to the physicians throughout the state to study all such materials forwarded to the laboratory, together with an offer to send them shipping containers. It is very gratifying to report that the laboratory staff in carrying out this work have confirmed the published researches on poliomyelitis and our hopes at one time were greatly encouraged by a rather constant finding of a microorganism which we were unable, until recently, to grow in pure culture, in the blood of children suffering with the disease and in the blood of monkeys suffering from this disease.

Details of these reports were published from the laboratory in March, 1911. At that time we claimed nothing more than that the organism was found with great regularity in the stained blood of human and experimental poliomyelitis. The only thing new to add concerning it at this time is its demonstrated motility. We are continuing work with a series of experiments and continually propagating several strains of virus with the hope that at some time we will learn what its etiologic significance may be.

## RESULTS OF INTENSIVE STUDY OF 748 CASES

An intensive study was undertaken by the department, resulting in a more or less complete record of 748 cases, giving details of physical conditions of the premises in which the patient sickened, the history of any possible exposure either to human cases of this disease or to domestic animals that may have had paralysis, the notes being so complete as to include possible exposure to flies, ticks, mosquitos, ants or any biting insect; exposure to heat, cold or dampness; exposure through swimming, wading or paddling and exposure to dust. A detailed clinical record was secured from the greater number of these cases giving the duration of the fever, the average range of fever, pulse-rate, date of onset of paralysis; full notes as to other cases in the family or neighborhood, a note of the extent of the paralysis at the height of the disease, and finally a note of the extent of residual paralysis existing several months after all symptoms of acute illness had subsided.

We are very greatly indebted to upward of 600 physicians practicing in the commonwealth for all of these detailed records, the compilation of which would not have been possible but for their loyal cooperation.

Detailed epidemiologic records were forwarded by 605 physicians, covering 748 cases.

| | | | | |
|---|---|---|---|---|
| 528 | physicians | reported | 1 case | each |
| 45 | physicians | reported | 2 cases | each |
| 17 | physicians | reported | 3 cases | each |
| 7 | physicians | reported | 4 cases | each |
| 4 | physicians | reported | 5 cases | each |
| 1 | physician | reported | 6 cases | |
| 2 | physicians | reported | 8 cases | each |
| 1 | physician | reported | 10 cases | |

A few interesting observations may be summarized from the many points developed in this intensive study.

Out of 773 cases of poliomyelitis, fifty-nine gave a distinct history of exposure to previous cases, the sexes being equally divided. Nationality seems to play no particular part in this disease, the vast majority of those contracting poliomyelitis being American-born. Males have more frequently contracted the disease than females. Out of this series of cases 437 were males, and 336 were females. But three of the colored race (two males and one female) sickened. In forty-four instances secondary cases developed in the household.

Other acute illnesses two months prior to the development of infantile paralysis seemed to show but little influence. In three instances whooping-cough existed; in three, intestinal indigestion; in five, measles; in ten, diarrhea; in thirteen, gastro-enteritis; in four, influenza; in nine, tonsillitis; in four, acute enteritis.

Great exposure to heat, cold and dampness was noted in comparatively few instances. Great heat was recorded in sixty-five cases; exposure to cold in twenty-seven; exposure to dampness in eighty-nine.

A total of thirty patients are reported to have met with some minor accident a short time previous to the onset of poliomyelitis.

It was somewhat surprising to find over-exertion reported so seldom, a total of twenty-eight cases being recorded, twenty in the male sex, the exertion often consisting of hard work in the open field.

In nineteen cases a history of automobile riding was noted; in sixteen, swimming; in twenty-nine, wading in open streams; in thirty-seven, paddling in water; in 157 instances the individual contracting the disease constantly ran barefoot.

The prevalence of other diseases in the community during the outbreak of poliomyelitis was not as great as has been reported by some authorities. The diseases of particular moment frequently recorded in infected communities were tonsillitis twenty-five times, gastro-intestinal disturbances forty-seven times.

The date of onset by months is of peculiar interest. Occasional deaths from this disease were recorded during the early months in the year, one in January, two in February and two in April. The disease apparently became more frequent the latter half of June, in each instance in communities where patients had died from the infection at some time during the winter months. In June twenty-four cases were reported; in July 120; in August 262; in September 230; in October 130; in November forty-one; in December ten; a total of 1,076 cases being reported to the department during the twelve months.

By action of the Advisory Board of the State Department of Health, poliomyelitis was made reportable Jan. 7, 1910, general advertisement of the regulation taking place immediately, but individual notices were not mailed to physicians until July, so it is possible that some cases were not reported in the first half of the year. A total of 240 certificates were filed with the department giving poliomyelitis as the cause of death. This mortality shows the disease to have been unusually virulent, even grant-

ing that a good many cases may have been missed because it had been so recently made reportable.

The average duration of the fever was about four days. The series of cases studied carefully from the family physicians' notes show that in fourteen cases the fever lasted less than twenty-four hours; in thirty-five, two days; in sixty-eight, three days; in sixty-five, four days; in seventy-two, five days; in thirty-four, six days; in 137, one week and over; in eighty cases, two weeks and over.

The temperature range averaged 99 to 104 + F., the records in twelve cases showing 99 to 100; in fifty-four it was 100 to 101; in 106 cases, 101 to 102; in 147 cases, 102 to 103; in 119 cases, 103 to 104; in sixty-five cases, 104 and over.

The pulse-rate was increased in a large percentage of the cases, the average rate being near 100. In twenty-two instances a record is made of a rate above 150. In a vast majority of the cases the pulse tension is given as high.

In tabulating the symptoms present during the onset and early stage of the illness we find irritability present in 372 cases; stupor in 225; nausea in 343; vomiting in 366; retraction of head in 267; retraction of back in 192; nervous twitchings in 345; convulsions in sixty-one; diarrhea in 159; constipation in 349; retention of urine in 118; incontinence of urine in ninety-seven; insomnia in 291; sleepiness in 244, and sore throat in 101 cases. These symptoms seem to apply with great uniformity to both sexes.

Skin eruption was recorded in sixty-three instances. A scarlatiniform erythema was described several times.

It is worthy of note that the presence of pain and tenderness was recorded in 564 cases of the 773 studied intensively. In a very large majority of the cases pain was most severe in the area of the body later showing paralysis and the pain usually subsided on the appearance of paralysis. A greater number of patients complained of pain in the spinal region alone than in any other area of the body, a total of sixty-nine having pain in this region only. Fifty-one complained of spinal and lumbar pain, and in addition, of pain in all extremities. Thirty-three complained of pain in the lumbar region only, nineteen of pain in the cervical region and a total of thirty-seven complained of pain in the large joints, shoulders, hips or elbows; two complained of it in the left thigh only, three in the right thigh, one in the left hand, one in both feet and

one in the right foot only. Abdominal pain was not frequent except as associated with nausea and vomiting.

In a few instances (thirty-four) evidence of insect bites was noted. Particulars of these marks will be found in another part of the paper.

In this series of 773 cases, 142 patients (18.4 per cent.) recovered without paralysis and 294 (71.6 per cent.) recovered with considerable residual paralysis.

The distribution of paralysis when at its height presents some interesting features, the following table showing how frequently the extremities alone were involved:

| Extremity | Times involved | Extremity | Times involved |
|---|---|---|---|
| Left arm only | 16 | Both legs only | 120 |
| Right arm only | 20 | Left hemiplegia | 35 |
| Left leg only | 74 | Right hemiplegia | 42 |
| Right leg only | 69 | All four extremities | 78 |
| Both arms only | 4 | | |

In addition to the seventy-eight instances in which the four extremities were involved, additional parts were paralyzed as follows:

All extremities and both eyes.....Once
All extremities, right eye and right face.....Once
All extremities, left eye and neck.....Once
All extremities, back and abdomen.....Once
All extremities, left face, left eye, neck, back and abdomen.....Once
All extremities and both eyes.....Once
All extremities, neck, back and abdomen.....Once
All extremities, neck, back, abdomen and left face.....Once

In addition to the 120 cases having both legs only paralyzed, the following cases had additional parts involved:

Both legs and right face.....Once
Both legs, right arm and abdomen.....Once
Both legs, back and abdomen.....Once
Both legs, right face, right eye and right forearm.....Once
Both legs and right arm.....3 times
Both legs and left arm.....Once
Both legs, right arm and right face.....Once
Both legs, right arm and neck.....Once
Both legs, right arm, right eye and right face.....Once

Crossed paralysis was found as follows:

| | |
|---|---|
| Right upper extremity and left lower extremity | 6 times |
| Left upper extremity and right lower extremity | 5 times |

In thirty-four instances one or both legs were paralyzed, either alone or in combination with some other part of the body.

In nineteen the right face was paralyzed twice with only the eye or eye and neck involved, and seventeen cases in connection with some other parts of the body.

The left face was involved in twenty-two cases, always in connection with some other part of the body.

Impairment of intelligence was noted in twenty-nine instances.

Housing conditions show that in 149 instances the individual sickened in a large home; in 219 instances in a medium sized home, and in 164 instances in a small dwelling.

When classified with reference to the number of members of the household the tabulation shows two instances in a family of one; thirteen in a family of two; eighty-six in a family of three; 154 in a family of four; 121 in a family of five; ninety-five in a family of six; sixty-two in a family of seven; thirty-three in a family of eight; twenty-three in a family of nine; twenty-three in a family of ten and over.

With reference to the number of children in the household, the tabulation shows 106 instances in which there was one child; 174 in which there were two children; 110 in which there were three children; ninety in which there were four; fifty-nine in which there were five; twenty-two in which there were six; seventeen in which there were seven; twenty in which there were eight; five in which there were nine; four in which there were ten and over; eighteen in which there were none, with 148 unstated cases.

Out of 773 cases contact occurred as follows:

| | |
|---|---|
| Certain direct contact with acute case | 59 |
| Certain direct contact with abortive case | 7 |
| Certain direct contact with chronic case | 2 |
| Certain direct contact with acute case by second person | 5 |
| Adults exposed escaping paralysis | 1,678 |
| Children exposed, escaping paralysis | 1,062 |
| Children sleeping in same bed room with acute case, escaping paralysis | 261 |

These figures establish the fact that the danger of transmission from one member of the household to another member of the same household

Fig. 1.—Photomicrograph of pure culture of microorganisms found in the blood of patients with acute anterior poliomyelitis, showing long and short forms of the organism.

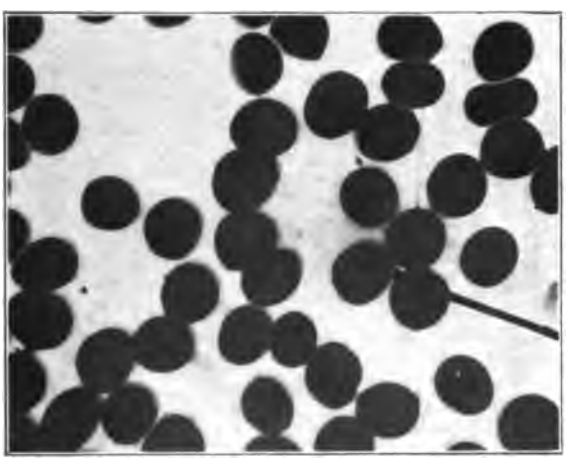


Fig. 2.—Photomicrograph of blood of patient ill of acute anterior poliomyelitis, showing a single organism with bulbous ends connected by a long thin body, attached at one end to red corpuscle in exact center of photograph.

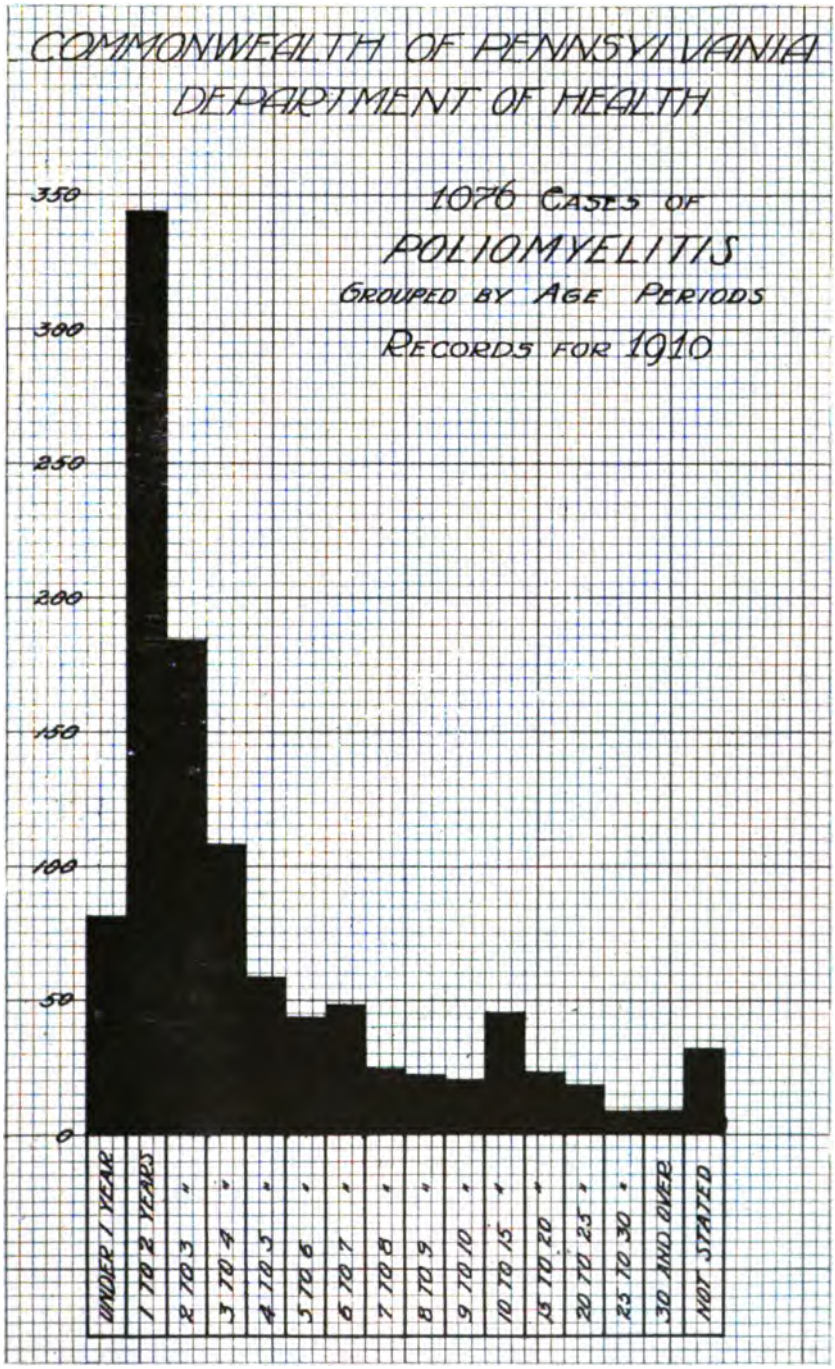



Fig. 3.—Chart showing graphically the cases of poliomyelitis recorded in 1910, grouped by age periods.

is not great and when we consider the number of instances in which other children slept in the same bed-room with the child contracting poliomyelitis, it seems still more remarkable that so few secondary cases occurred. In 289 instances children slept in the same bed-room, only twenty-four contracting the disease.

In nine instances the disease developed in children after having visited communities where this disease was known to be prevalent. In five cases the possibility of transmission through a second individual seemed probable. These will be given in detail with the case history. In a number of instances suggestive illness occurred in the same household with frank cases of paralysis. A few such cases will be cited with their histories.

Further studies of household conditions showed that in 390 homes doors and windows were screened. In 128 homes sanitary conditions are classified as excellent; in 215 homes as good; in 226 as fair; in sixty-six as bad, with 138 unstated.

Mosquitoes were reported as having access to the house 324 times.

The dwelling stood near a stable or barn in 297 instances; near a poultry house 289 times; near a privy 275 times; and forty-seven times a public garbage dump is reported near the residence. Stagnant water nearby is reported seventy-five times; near open streams in 171 instances; near open drains in 140 instances.

In 410 instances trees are reported in the immediate vicinity of the dwelling; in 122, shrubbery. The particular trees enumerated will be found in a table.

Sanitary plumbing is reported in 277 homes; outside closets in 476.

Household garbage was disposed of to hogs on the premises in thirty-six instances; was burned in thirty-eight; a public system of disposal was reported 231 times; was buried in four instances; thrown on surface of ground 162 times; fed to other domestic animals eleven times.

The water-supply to the household was given as public in 327 instances; well in 194 instances; spring in sixty instances and cistern in thirty-three instances.

The ice-supply was given as natural in eighty-four instances; artificial in 164 instances; none used at all in 322 instances; with 203 unstated.

The milk-supply was given as one cow in 167 instances; breast-fed in twenty-five instances; condensed in five instances; in bottles in 194 instances; in cans in 112 instances; in own receptacles in twenty instances.

Fruits and vegetables used prior to illness in the various households and partaken of by those ill may be well summarized in the following table:

| | | | |
|---|---|---|---|
| Common varieties | 117 | Watermelon | 2 |
| Cabbage | 15 | Canteloupe | 3 |
| Potatoes | 19 | Pineapple | 1 |
| Lima beans | 4 | Grapefruit | 1 |
| String beans | 6 | Bananas | 51 |
| Peas | 10 | Oranges | 47 |
| Parsnips | 1 | Peaches | 36 |
| Carrots | 1 | Apples | 115 |
| Tomatoes | 28 | Green apples | 1 |
| Corn | 8 | Plums | 20 |
| Parsley | 1 | Grapes | 14 |
| Cucumbers | 3 | Green grapes | 2 |
| Celery | 7 | Cherries | 15 |
| Radishes | 9 | Berries | 21 |
| Onions | 17 | No vegetables used | 116 |
| Lettuce | 18 | Not stated | 55 |

Vermin were reported as follows:

| | Houses |
|---|---|
| Flies were present in | 383 |
| Mosquitoes were present in | 212 |
| Mice (house) were present in | 149 |
| Rats were present in | 77 |
| Ants were present in | 85 |
| Roaches were present in | 90 |
| Bedbugs were present in | 91 |
| Spiders were present in | 127 |
| Mice (field) were present in | 43 |
| Biting flies were present in | 169 |
| Ticks were present in | 14 |

TABLE 1.—POLIOMYELITIS GROUPED BY AGE PERIODS

| | Cases | | Cases |
|---|---|---|---|
| 1 month | 2 | 3 to 4 years | 108 |
| 2 months | 1 | 4 to 5 years | 58 |
| 3 months | 4 | 5 to 6 years | 44 |
| 4 months | 4 | 6 to 7 years | 50 |
| 5 months | 7 | 7 to 8 years | 24 |
| 6 months | 9 | 8 to 9 years | 22 |
| 7 months | 12 | 9 to 10 years | 20 |
| 8 months | 7 | 10 to 15 years | 45 |
| 9 months | 20 | 15 to 20 years | 23 |
| 10 months | 7 | 20 to 25 years | 18 |
| 11 months | 8 | 25 to 30 years | 8 |
| 1 to 2 years | 346 | 30 years and over | 8 |
| 2 to 3 years | 187 | Not stated | 34 |
| | | Total | 1076 |

TABLE 2.—DAY OF ONSET OF PARALYSIS

| | Cases | | Cases |
|---|---|---|---|
| Same day | 111 | 10 days | 8 |
| 1 day | 83 | 11 days | 4 |
| 2 days | 88 | 12 days | 2 |
| 3 days | 93 | 13 days | 0 |
| 4 days | 51 | 14 days | 3 |
| 5 days | 37 | 15 days | 2 |
| 6 days | 22 | 19 days | 1 |
| 7 days | 22 | 20 days | 1 |
| 8 days | 9 | 21 days | 5 |
| 9 days | 5 | Not stated | 126 |

Trees and shrubbery stood near the infected house as follows:

| Trees | | Shrubbery | |
|---|---|---|---|
| Fruit | 168 | Roses | 26 |
| Maple | 150 | Grape Vine | 10 |
| Poplar | 30 | Lilacs | 8 |
| Oak | 21 | Honeysuckle | 6 |
| Pine | 11 | Hedge | 3 |
| Willow | 9 | Vines | 1 |
| Locust | 9 | Snow-balls | 1 |
| Chestnut | 9 | Locust | 1 |
| Horse-chestnut | 9 | Japanese hop vine | 1 |
| Elm | 4 | Cedar | 1 |
| Beech | 4 | Berry | 1 |
| Walnut | 3 | Scrub-apple | 1 |
| Linden | 2 | Maple | 1 |
| Cottonwood | 2 | Mock-orange | 1 |
| Cedar | 2 | Clematis | 1 |
| Birch | 1 | Underbrush | 1 |
| Spruce | 1 | Privet and thorn hedge | 1 |
| Shumac | 1 | Kind not stated | 52 |
| Ash | 1 | | |
| Kind not stated | 23 | | |

DATA AS TO DOMESTIC ANIMALS

240 homes had dogs without sickness
264 homes had cats without sickness
254 homes had chickens without sickness
57 homes had birds without sickness
180 homes had horses without sickness
155 homes had cows without sickness
1 home had 1 dog with sickness
3 homes had chickens with sickness (paralysis)
1 home had 1 bird with sickness (paralysis)
1 home had 1 horse with sickness
1 home had 2 cats with sickness

### Insect Bites

Mosquito bites appeared in 15 cases as follows:

| | | | |
|---|---|---|---|
| Back | 1 | Body | 1 |
| Hands | 3 | Thighs | 1 |
| Face | 4 | Chest | 1 |
| Neck | 3 | Location not stated | 1 |

Bedbug bites appeared in 2 cases as follows:

| | | | |
|---|---|---|---|
| Thighs | 1 | Chest | 1 |

Unknown insect bites appeared in 17 instances as follows:

| | | | |
|---|---|---|---|
| Face | 4 | Thighs | 2 |
| Neck | 2 | Temporal region | 1 |
| Body | 4 | Location not stated | 3 |
| Head | 1 | | |

In many histories rats were reported on the premises. Field mice were frequently found. In 149 homes house mice were prevalent; in 383 homes ordinary flies were found; biting flies were reported 169 times; bedbugs ninety-one times; roaches ninety times; ticks fourteen times; ants eighty-five and spiders 127. Mosquitoes were noted in 212 instances.

Unusual insects were reported in eighteen instances, particulars being found elsewhere.

In three instances paralytic disease occurred in animals, the particulars being set forth elsewhere.

The underclothing worn by those sickening is reported as being cotton in 304 cases; woolen in eighty-two; half cotton and half wool in ten. The stockings were reported as being cotton in 300; woolen in seventy-eight; half cotton and half wool in six.

Several centers of unusual prevalence were noted, one in the vicinity of Galeton near the line between Potter and Tioga Counties, at a great elevation in the northern part of the state; one in the vicinity of the Bethlehems and Allentown in Northampton and Lehigh Counties in the east central section of the state; one in Lancaster County in the city of Lancaster and adjacent rural districts in the south central part of the state and one each in Luzerne and Westmoreland Counties in the southwestern section of the commonwealth, and in Philadelphia county in the section of the city known as Germantown and in a part of West Philadelphia west of the Schuylkill River. The disease was found, however, in fifty-eight counties out of sixty-seven. Grouped by counties the following table shows the distribution throughout the state:

TABLE 3.—SHOWING DISTRIBUTION OF CASES AND POPULATION

| County | Cases | Population | County | Cases | Population |
|---|---|---|---|---|---|
| Adams | 0 | 34,319 | Lancaster | 150 | 167,029 |
| Allegheny | 89 | 1,018,463 | Lawrence | 4 | 70,032 |
| Armstrong | 7 | 67,880 | Lebanon | 3 | 59,565 |
| Beaver | 17 | 78,353 | Lehigh | 101 | 118,832 |
| Bedford | 1 | 38,879 | Luzerne | 15 | 343,186 |
| Berks | 26 | 183,222 | Lycoming | 4 | 80,813 |
| Blair | 0 | 108,858 | McKean | 15 | 47,868 |
| Bradford | 4 | 54,526 | Mercer | 2 | 77,699 |
| Bucks | 27 | 76,530 | Mifflin | 4 | 27,785 |
| Butler | 14 | 72,689 | Monroe | 6 | 22,941 |
| Cambria | 3 | 166,131 | Montgomery | 33 | 159,590 |
| Cameron | 2 | 7,644 | Montour | 1 | 14,868 |
| Carbon | 10 | 52,846 | Northampton | 140 | 127,667 |
| Centre | 4 | 43,424 | Northumberland | 7 | 111,420 |
| Chester | 11 | 109,213 | Perry | 5 | 24,136 |
| Clarion | 0 | 36,638 | Pike | 1 | 8,033 |
| Clearfield | 1 | 93,768 | Potter | 9 | 29,729 |
| Clinton | 0 | 31,545 | Schuylkill | 15 | 207,894 |
| Columbia | 7 | 48,467 | Snyder | 1 | 16,800 |
| Crawford | 1 | 61,565 | Somerset | 7 | 67,717 |
| Cumberland | 4 | 54,479 | Sullivan | 0 | 11,293 |
| Dauphin | 11 | 136,153 | Susquehanna | 0 | 37,746 |
| Delaware | 16 | 117,906 | Tioga | 19 | 42,829 |
| Elk | 2 | 35,871 | Union | 1 | 16,249 |
| Erie | 8 | 115,517 | Venango | 4 | 56,359 |
| Fayette | 19 | 167,449 | Warren | 1 | 39,592 |
| Forest | 0 | 9,435 | Washington | 21 | 143,680 |
| Franklin | 6 | 59,775 | Wayne | 3 | 29,236 |
| Fulton | 0 | 9,703 | Westmoreland | 50 | 231,304 |
| Greene | 1 | 28,882 | Wyoming | 2 | 15,509 |
| Huntingdon | 1 | 38,304 | York | 6 | 136,405 |
| Indiana | 5 | 66,210 | Philadelphia | 143 | 1,549,008 |
| Jefferson | 2 | 63,090 | | | |
| Juniata | 0 | 15,013 | | 1076 | |
| Lackawanna | 4 | 259,570 | | | |

It is interesting to note that few cases developed in Elk, Venango and Clearfield Counties, where epidemics were reported in 1907, and in Adams County, where a small outbreak occurred in 1908. The exception, however, occurred in Butler County, where a few cases developed in 1907, and fourteen cases in 1910.

The laboratory staff, working from the branches opened in the field, made an intensive study of seventy-three cases during life and a study of pathologic materials from eleven fatal cases, doing a great deal of routine work resulting in statistics too elaborate to refer to more than incidentally in this paper. A composite table of blood-counts alone,

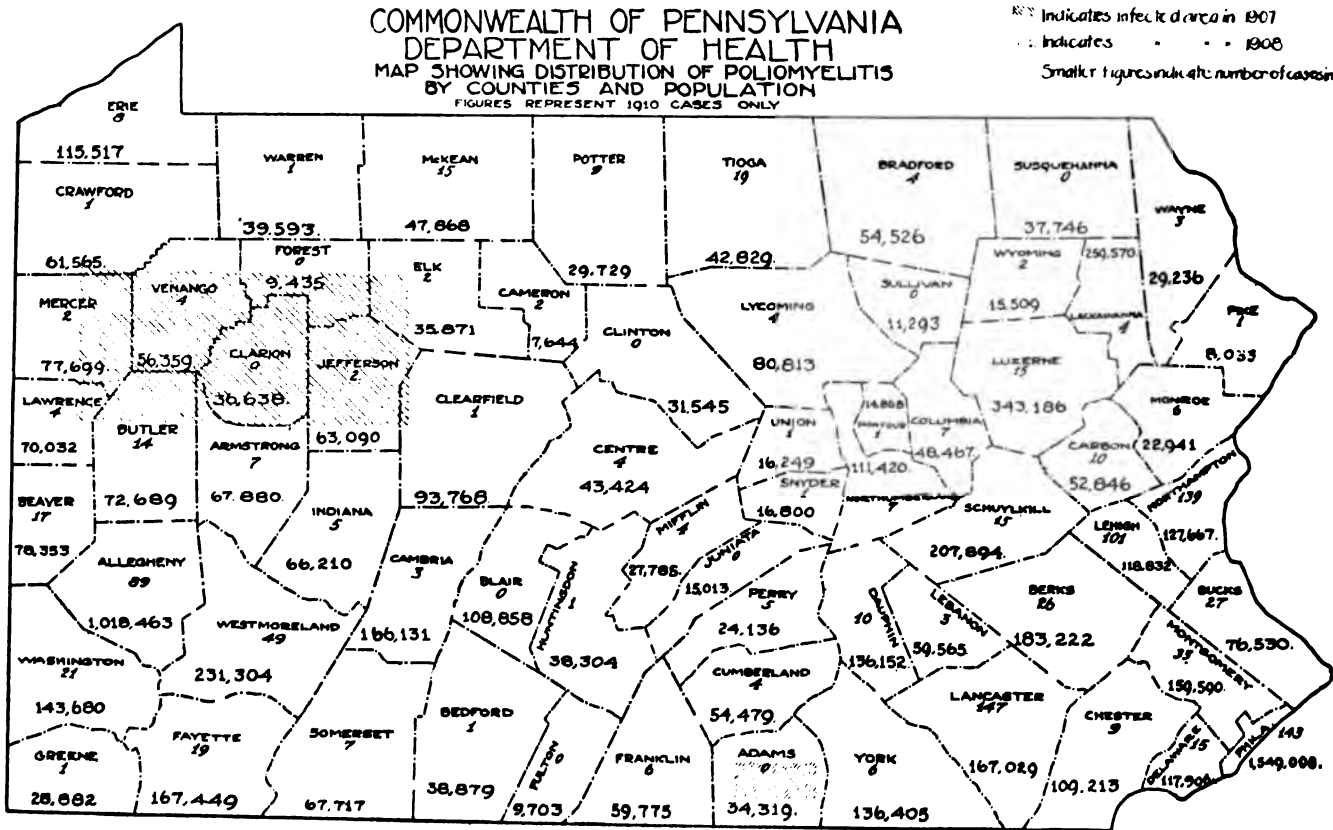



Fig. 4.—Map showing distribution of the disease, and also the population of the counties. The area indicated by broken black lines shows the district in northwestern Pennsylvania affected in 1907 and the district in Adams county affected in 1908.

when grouped by day of disease on which count was made, is worthy of reproduction.

| Day | Polynuclears | Small Lymphocytes | Large Lymphocytes | Eosinophils |
|---|---|---|---|---|
| 2nd to 5th | 52.2 | 34.2 | 10.1 | 3.5 |
| 6th to 9th | 47.2 | 34.6 | 13.2 | 5. |
| After 10th | 51.4 | 32.8 | 13.1 | 2.7 |

Ordinary leukocyte counts were made in a series of cases. The results seem to show a high degree of leukocytosis up to the ninth day of illness. Spinal fluids were studied eleven times, in each instance fluid being secured during the active stage of the disease. Neutral broth cultures showed the common diplococcus in every such fluid, but in no instance were we able to secure paralysis by inoculation with this organism.

A very large number of swabbings from the nasopharynx were secured and from fourteen such swabbings attempts were made to inoculate five monkeys by applying the centrifugal sediment resulting from macerating these materials in salt solution, swabbing the sediment over the mucous membranes and as nearly as possible placing sediment over the cribriform ethmoidal plate. All of these results were negative.

Six monkeys and seven rabbits injected under the skin with this material gave negative results. These findings seem to show that there is not great danger from the discharges, even though we do succeed in producing the disease by using the actual mucous membranes in the nasopharyngeal area.

Inoculation experiments made in an attempt to produce immunity in monkeys was to a very high degree successful. Attempts to give the disease to rabbits was only in part successful, as we failed absolutely in our attempts to transmit the disease from the rabbit developing paralysis to other rabbits or back to monkeys. It is possible that failure in this experiment occurred because the paralysis in the rabbit was not demonstrable until two weeks after inoculation.

In several communities an unusual number of yellow butterflies were reported. A series of these butterflies were collected, killed and macerated. Inoculation experiments from the resulting material failed uniformly to produce paralysis.

In the Bethlehems a blight among Norway maple trees attracted considerable attention and it was thought by many citizens that this disease was more prevalent near houses where cases of poliomyelitis

TABLE 4.—SHOWING DETAILS OF CONTACT CASES

| No. | Name | Contact | Manner | Same House | Date of Contact | Onset of Paralysis |
|---|---|---|---|---|---|---|
| 160 | J. Z. | From Trenton, N. J., direct contact in Lancaster on July 19. Indirect contact through father July 20 | Direct and Indirect | No | July 19-20 | July 20 |
| 20 | H. H. | E. V. Philadelphia | Direct | No | 3 yrs. or less | July 1 |
| 733 | L. H. | D. F. | Direct | No | July 14 | July 23 |
| 315 | C. S. | N. D. | Direct | No | Aug. 24 | Sept. 1 |
| 188 | J. C. S. | H. G., New Brighton | Direct | No | Aug. 21 | Sept. 1 |
| 1 | M. M. | M. M. | Direct | No | July 27 | Aug. 10 |
| 34 | C. D. | K. L. | Direct | No | Aug. 26 | Sept. 9 |
| 17 | M. C. | [illegible]. T. | Direct | No | July 10 | Aug. 24 |
| 715 | A. E. | G. E. | Direct | Yes | Sept. 1 | Sept. 10 |
| 499 | F. O. | Case in same house | Direct | Yes | Aug. 5 | Aug. 25 |
| 319 | W. R. | Brother | Direct | Yes | Unstated | Aug. 9 |
| 577 | C. H. | Brother | Direct | Yes | Aug. 25 | Sept. 3 |
| 296 | J. N. | Several cases in Scranton | Direct | No | July 3 | July 10 |
| 492 | W. G. | 1619 Chew St. | Direct | No | July 10 | July 12 |
| 501 | J. K. | Neighbor | Direct | No | July 12 | July 26 |
| 255 | B. W. | S. H. | Direct | No | Aug. 18 | Aug. 25 |
| 390 | L. E. L. | Child. Smock, R. F. D. | Direct | No | Oct. 19 | Nov. 2 |
| 670 | J. S. | Philadelphia (L. children) | Direct | No | June 21 | July 1 |
| 700 | N. Y. | A. Y. | Direct | Yes | Constant | Sept. 27 |
| 704 | W. Y. | A. Y. | Direct | Yes | Constant | Sept. 30 |
| 691 | F. C. | E. F. | Direct | Yes | Constant | Aug. 7 |
| 696 | S. B. | K. B. | Direct | Yes | Oct. 8 | Oct. 11 |
| 693 | H. R. | H. R., N. Bethlehem | Direct | Unstated | June 20 | July 7 |
| 847 | F. S. | Other case in family | Direct | Yes | Unstated | July 25 |
| 846 | R. S. | F. S. | Direct | Yes | July 25 | July 29 |
| 446 | M. U. | J. C. (Slept in same bed) No. 527 | Direct | No | June 15 | June 26 |
| 261 | M. H. | W. H. | Direct | Yes | July 24 | Aug. 1 |
| 268 | L. M. | Case 1067 | Direct | Yes | Constant | Aug. 15 |
| 239 | G. C. | K. C. | Direct | Yes | Constant | Sept. 11 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 610 | L. H. | N. H. | Direct | Yes | Aug. 17 | Aug. 24 |
| 94 | A. R. | M. R. | Direct | Yes | Oct. 31 | Nov. 4 |
| 234 | M. O. | C. O. (Case 554) | Direct | Yes | Constant | Sept. 3 |
| 329 | F. O. | C. O. (Case 554) | Direct | Yes | Constant from 8/23 | Sept. 2 |
| 342 | M. W. | R. W. (Case 338) | Direct | Yes | Constant | Sept. 19 |
| 666 | W. A. | Brother (Case 665) | Direct | Yes | Aug. 24 | Sept. 8 |
| 602 | M. H. | Brothers and sisters | Direct | Yes | Aug. 1 | Aug. 7-8 |
| 585 | C. E. | Sister | Direct | Yes | Aug. 1 | Aug. 8 |
| 434 | D. G. | Child from Huttles, Pa. | Direct | Yes | July 15 | Aug. 11 |
| 743 | H. W. | While waitress served a baby short time before who died from disease | Direct | No | Unstated | Oct. 5 |
| 1040 | P. S. | Brother | Direct | Yes | Aug. 2 | Aug. 9 |
| 2 | M. M. | Visit of mother to other case | Indirect | No | Sept. 24 | Oct. 13 |
| 393 | P. C. | Grandmother from Lancaster ten days prior former contact with case | Indirect | No | Sept. 21 | Oct. 1 |
| 606 | — D. | Mother ironed Huber family wash. Case 602.. | Indirect | No | Aug. 1-8 inc. | Aug. 12 |
| 269 | B. T. | Cases in neighborhood | Indirect | No | Unstated | Sept. 15 |
| 231 | A. H. | Cases within a mile | Indirect | No | Unstated | Aug. 1 |
| 201 | N. K. | Came from Trenton week previous to June 5.. | Indirect | No | Unstated | July 7 |
| 27 | D. A. | Other case in neighborhood | Indirect | No | Unstated | Aug. 5 |
| 234 | N. H. | Visited Lancaster Co. | Indirect | No | Sept. 25 | Oct. 1 |
| 109 | A. S. | Colerain Twp. Lancaster Co. | Indirect | No | About Aug. 1 | Aug. 18 |
| 304 | J. D. | In Pottstown prior to Sept. 24. In Elizabeth from Sept. 24 to 26 | Indirect | No | Prior to Sept. 26 | Oct. 1 |
| 657 | J. C. | Allentown on or about Sept. 20 | Indirect | No | Unstated | Oct. 1 |
| 325 | C. W. | B. family | Indirect | No | Unstated | Sept. 20 |
| 357 | F. T. | R. M. milk from M. cow | Indirect | No | Constant and Unstated | Oct. 14 |
| 385 | E. Y. | M. case | Indirect | No | Unstated | Nov. 4 |
| 184 | M. B. | Philadelphia | Indirect | No | Unknown | Aug. 8 |
| 363 | B. S. | J. S. Brookville, R. D | Unstated | No | Aug. 1 | Dec. 1 |
| 403 | M. B. | S. V. Snedekerville, Pa. | Unstated | No | Sept. | Oct. 1 |

existed. A careful examination of these conditions showed that the blight was not confined to the Norway maple and that there was no greater involvement of trees in the vicinity of the affected houses than elsewhere. Examination of the blighted branches showed a delicate mycelium running through the mesophyl of the leaves that was not identical with the oidium of Westphalia. The study of this mycelium gave us negative results. A large number of specimens of blood smears, samples of feces, urine and nose and throat swabbings were sent us by practitioners, but aside from finding microorganisms in the blood with great uniformity, nothing worthy of note was seen.

EXTRACT FROM LABORATORY REPORT PUBLISHED MARCH 2, 1911

In examining the blood from acute cases of poliomyelitis in human beings, and also in monkeys in which the disease was produced experimentally, an organism was found, different in morphologic characteristics from any heretofore described which may or may not, on further investigation, prove to be the etiologic factor in the causation of the disease. Blood smears being fixed in methyl alcohol for one minute and stained with carbol-thionin, the organism appears as a faintly-stained blue rod with regular cell wall about 10 microns long and about 8 microns in width, curved at an angle of 60 to 75 degrees at one end, occasionally at both ends. At times, the curved end is bulbous. Some of the organisms appear to have a very finely granular protoplasm when the highest amplification is employed. They may be discerned by means of a 4 mm. dry objective but their characteristics are much more satisfactorily delineated under the 1/12 oil-immersion lens. They are found free in the serum as well as within the body of the red blood-cell.

The organisms do not retain the violet color when stained by the method of Gram but assume the color of the counter stain which, as generally used in this laboratory, is a very dilute solution of carbol-fuchsin.

The bloods examined were from ten different cases of acute poliomyelitis in children and were taken during the epidemic of last summer and autumn, and from thirteen cases of the disease during the acute stage, which had been produced experimentally in as many monkeys.

Blood smears from three normal human beings were carefully examined and although the search for these organisms was diligently made, none was found. Smears were made from the bloods of thirteen normal monkeys with negative results. After inoculation with the virus these same monkeys gave positive results. The blood of other normal monkeys gave negative results.

Blood smears were stained with iodin and sulphuric acid in order to test the organisms for cellulose, but no blue stained organisms were seen.

Smears from the cords and brains of paralyzed monkeys, and from one human case were examined, but none of the new organisms was found.

Filtered virus stained with carbol-thionin and by Gram's method showed none of these organisms.

Defibrinated blood, three weeks to two months old, from two paralyzed monkeys, showed the forms in increased numbers.

**Cultures made from the blood of a paralyzed monkey, in blood bouillon, plain bouillon, and blood-agar, examined after having been inoculated three weeks, showed the presence of the organism in increased numbers. Dorsett's egg medium was inoculated with the same blood at the same time but the organism was not found in smears from the surface of the medium or from the water of condensation.**

### SUBSEQUENT FINDINGS

Since publishing the above preliminary report on the finding of rod-shaped microorganisms in specimens of stained blood taken from human beings suffering from poliomyelitis and from monkeys in which the disease had been produced experimentally, these microorganisms have been found moving freely in the serum or attached to the side of a red blood-corpuscle in fresh blood taken from three monkeys ill of poliomyelitis. The monkey blood was examined at the time of inoculation and at twenty-four-hour periods up to 168 hours after inoculation. In the blood examined at the time of inoculation and at the twenty-four-hour period no organisms were found. At the end of forty-eight hours, however, a few of the moving microorganisms were found. Their numbers in the fresh blood specimens were increased up to 120 hours, after which time they seemed to appear in about the same numbers till examination at regular intervals was discontinued. At the end of three weeks the motile organisms could still be found in large numbers in the fresh blood.

Examination of the blood of a normal monkey examined at the same period as a control, failed to reveal any of the microorganisms.

The motility was of a slow, sinuous type resembling that of a spirillum. The bulbous ends were readily discernible. At times the organism appeared as standing on end, presenting the bulb uppermost, so that it resembled a large coccus in the microscopic field. Presently it would right itself and the long curved rod terminating in this bulb could be distinctly followed.

Pure cultures of this organism were isolated from the bloods of these three monkeys, on a medium made of the central nervous system of a monkey, combined with agar-agar. After a generation or two on this central-nervous-system-agar, the organism grows well on the ordinary laboratory media.

### CHARACTERS OF THE ORGANISM

The morphologic, biologic and biochemic characters of the organism grown on artificial media are as follows:

The best stain to bring out the morphology is carbol-thionin, though Loeffler's alkaline methylene-blue, Giemsa, Wright's, Ziehl-Nielson, carbol-

fuchsin and Gram's method demonstrate the organism with no difficulty whatsoever. Stained with carbol-thionin the organism appears as a granulated rod, the young forms measuring 0.6 to 0.8 microns in width by 1 to 2 microns in length. The older forms may appear as long as 10 or 12 microns with a width of 0.6 to 0.8 microns. Many of the indeterminate forms appear as spirals with from two to four loose turns. The longer forms have in many instances bulbous ends which have somewhat the appearance of spores, though free spores have never been observed.

The organism is actively motile, having a single polar flagellum at one pole only. It has no demonstrable capsule, and it is decolorized by the method of Gram. Colonies on agar are circular, moist, convex, entire, 1 to 3 mm. in diameter. In color they are bluish gray by direct light, old colonies having a yellowish tinge by transmitted light. Their peripheries are translucent while their centers are thickened and appear yellowish-white. Microscopically they are brownish-white, with a finely granular translucent periphery, and an opaque, brown, grumous center.

Agar Slant: Bluish gray with a suggestion of greenish tinge in cultures three or four days old, moist, raised, regular edges, growth along whole length of streak. White beaded growth in stab.

Gelatin: White, beaded growth along needle track with nail-head, moist growth on surface. No liquefaction.

Potato: Moist, cream to brown, abundant.

Central-Nervous-System-Agar: Gray, moist, very abundant along entire path of inoculation.

Egg Medium (consisting of yolk only): Moist, very abundant, spreading, pinkish growth.

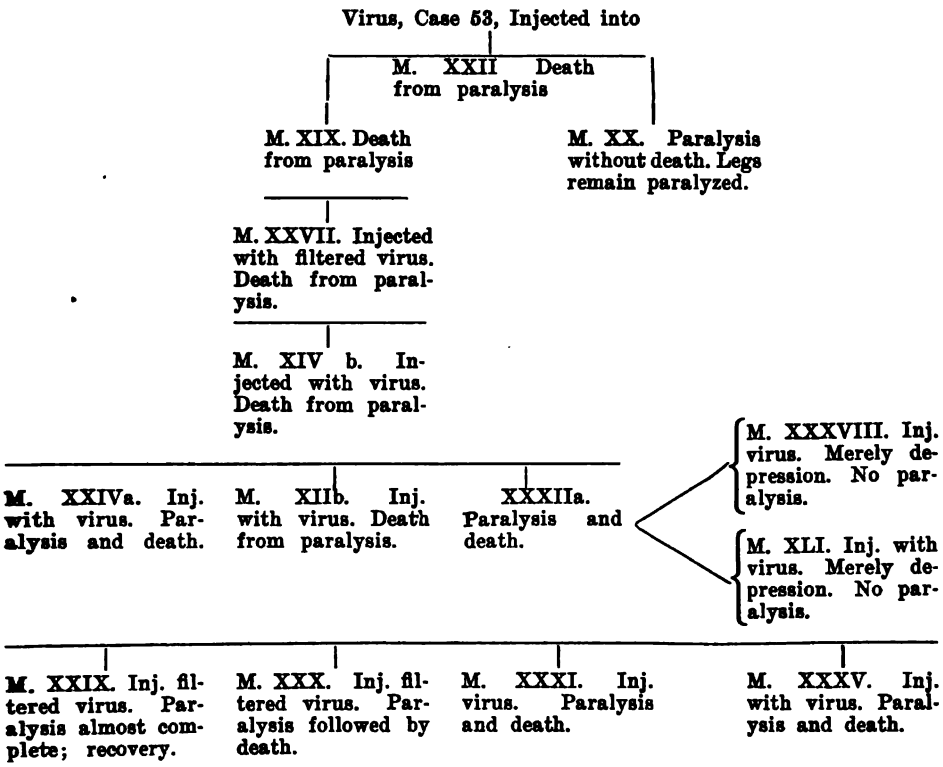
Bouillon: Very turbid, white flocculent sediment. In 120 hours a white ring around the glass tube at the level of the surface of the medium.

Litmus Milk: An initial acidity followed by a gradually increasing alkalinity, with a beginning reduction of the litmus at the bottom of the tube. No coagulation of the casein occurs. In four weeks acidification again takes place; reduction of litmus and firm coagulation after five weeks.

There is a slight production of acid in dextrose-agar and saccharose-agar, but not in mannite, maltose or lactose. Gas production does not occur in any of the sugars above mentioned. Mannite turns green after three weeks. The organism grows best in neutral medium, next best in acid, and poorest in alkaline.

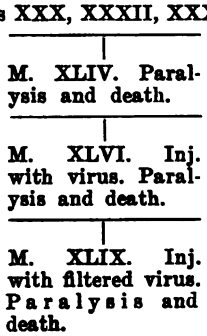
Indol is not produced. It seems to grow most abundantly on media rich in phosphates. It does not grow well on media containing much

TABLE 5.—SHOWING TRANSMISSIBILITY FROM HUMAN CASE TO MONKEY AND FROM MONKEY TO MONKEY


Virus, Case 53, Injected into
M. XXII Death from paralysis
M. XIX. Death from paralysis
M. XX. Paralysis without death. Legs remain paralyzed.
M. XXVII. Injected with filtered virus. Death from paralysis.
M. XIV b. Injected with virus. Death from paralysis.
M. XXIVa. Inj. with virus. Paralysis and death.
M. XIIb. Inj. with virus. Death from paralysis.
XXXIIa. Paralysis and death.
M. XXXVIII. Inj. virus. Merely depression. No paralysis.
M. XLI. Inj. with virus. Merely depression. No paralysis.
M. XXIX. Inj. filtered virus. Paralysis almost complete; recovery.
M. XXX. Inj. filtered virus. Paralysis followed by death.
M. XXXI. Inj. virus. Paralysis and death.
M. XXXV. Inj. with virus. Paralysis and death.

Filtrate of cords of human Case 53

Combined with Monkeys XXX, XXXII, XXXVIII, XLI and XXXV



glycerin. The organism grows in the absence of air as well as when the air is given free access.

EXPERIMENTAL PRODUCTION AND PREVENTION OF THE DISEASE

Experiments on the production of poliomyelitis in monkeys by using this organism are in progress.

We have published in connection with our laboratory work negative experiments resulting from a good many observations made with great care. On finding virus negative after an autopsy had been performed on a child dead with this disease, we conducted experiments to determine what agent in the embalming fluid might have been destructive, and, determining that formaldehyd and arsenic were both used in these fluids, a series of experiments were carried out with each, as well as with the fluid itself, solutions being injected at varying intervals as inoculation experiments to determine whether or not it would be possible to prevent the development of the disease by administration of these chemicals. The results in each instance were negative. Salvarsan was tried in a series of experiments in order that we might have data concerning the most potent arsenical preparation. These experiments, too, were negative, although they led to the incidental discovery of a positive Wassermann reaction in a monkey.

Abstract Case No. 256 (Laboratory Case No. 53).—G. T., female, aged 7; physician, Dr. George E. Day, Strasburg. Child well to August 23; August 24, stiffness of knee, pain in neck, fever, constipation, dizziness, temperature 102.5 F., no paralysis; August 26, paralysis right leg, both arms, loss of reflex, sensation normal; August 27, worse, pulse rapid, pressure symptoms; lumbar puncture secured 32 c.c. spinal fluid under excess pressure; August 28, slight improvement; 29th, breathing labored, 30th, death 9:00 a. m.; complete autopsy 11:00 a. m. Abundant material for laboratory study was obtained and true pathologic picture found. Tissues gave Noguchi butyric reaction. Emulsion from lumbar cord, bulb, pons, lymph-nodes, cultures from cerebrum, cerebellum, pons, bulb, lumbar cord, lymph-nodes; Gram positive coccus found in cultures taken at autopsy from brain and cord; nothing further by dark-field illumination. Monkeys inoculated with this coccus remained well. Two monkeys received emulsion from cord, pons and bulb into brain; both contracted disease and from this strain of virus successful transmission experiments were secured as illustrated on protocol of transmissibility.

I am greatly indebted to Dr. B. Franklin Royer, Chief Medical Inspector, and the staff of the Division of Medical Inspection, for the compilation of the statistics in this report, and to Drs. Herbert Fox, and J. B. Rucker, Jr., of the Laboratory Division, for the notes of the experimental work carried out under my direction.

# INFANTILE PARALYSIS

## WITH ESPECIAL REFERENCE TO ITS OCCURRENCE IN MASSACHUSETTS, 1907-1910 *

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BOSTON

The problem of infantile paralysis is definitely before the physicians of the United States.

In the twenty years from 1881 to 1900 there were reported in this country 200 cases. In the five-year period beginning in 1900 and ending in 1904 there were reported 100 cases. In the five years beginning in 1905 and ending in 1909, 5,400 cases, and in one — the year 1910 — approximately 9,000 cases. Such an extraordinary increase, in which Europe has in no way shared, brings before us very seriously our obligation to investigate the disease, to take account of our stock of knowledge regarding it and to do what we properly can do to quiet the panic that exists in the minds of the laity, by placing before them what we know and by asking their assistance to help us to learn more (Charts 1, 2 and 3).

The present paper will consist of a brief résumé of our present accepted knowledge of the various aspects of the disease and an analysis of the studies in Massachusetts made by the State Board of Health for the four years beginning in 1907.

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*This paper was prepared with the co-operation of Henry P. Walcott, M.D., Chairman of the Massachusetts State Board of Health, and of Theobald Smith, M.D., Milton J. Rosenau, M.D., John Lovett Morse, M.D., and James H. Wright, M.D., Advisory Committee on Infantile Paralysis to the Massachusetts State Board of Health.

In the field work the Board has had for two years (1909-1910) the services of Dr. Philip A. E. Sheppard of Boston, and Dr. Thomas P. Hennelly, now of Pittsfield, Mass. The epidemic in the Deerfield Valley in 1908 was investigated by Dr. Herbert P. Emerson, of Springfield, then State Inspector of Health for that district. Much valuable assistance has been rendered furthermore by the other State Inspectors of Health throughout the Commonwealth.

## I. RECENT HISTORY AND ETIOLOGY OF INFANTILE PARALYSIS
### RÉSUMÉ OF PRESENT ACCEPTED KNOWLEDGE

*History.*—The disease is not a new one. Although the first clear description of it was given in 1840 by Heine, a German, it was fairly well described by an English physician, Michael Underwood, in 1774. Since the perfectly clear description of the disease by Heine, in 1840,

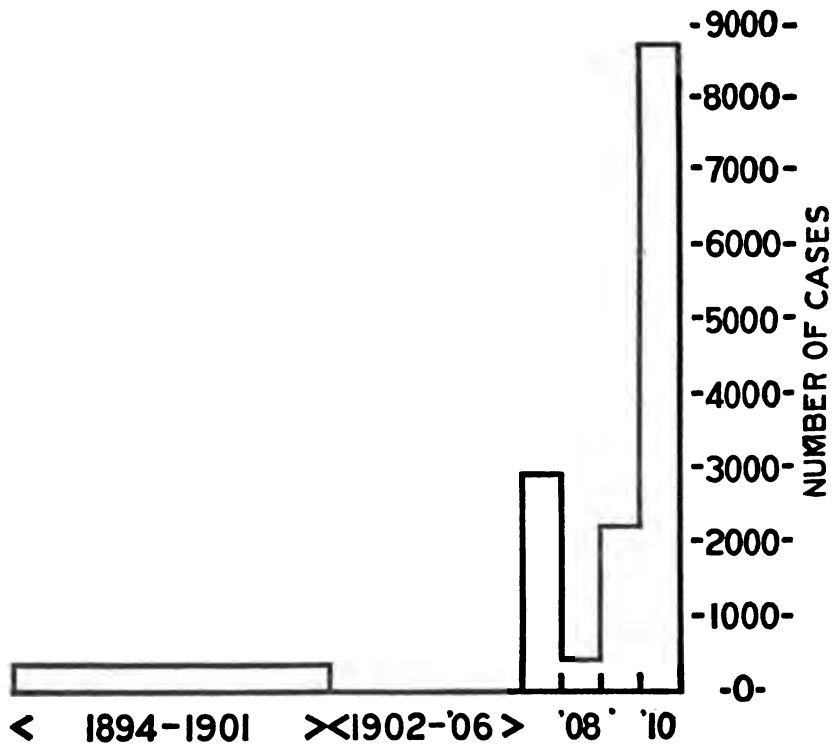



Chart 1.—Prevalence of infantile paralysis in the United States, 1894 to 1910.

successive additions to our knowledge have been made, the most important contributions until very recently having been by Norwegian and Swedish authors, who had unusual opportunities for the study of the disease between 1899 and 1907.

*Infectious Character.*—Although it had long been suspected to be an infectious disease, this fact was not absolutely proved until November, 1909, when Flexner and Lewis of the Rockefeller Institute in New York

demonstrated, by inoculation of a series of monkeys with tissues from children dying of the disease, that the process was an infectious one, placing it in the category with rabies, yellow fever and foot-and-mouth disease. This discovery was undoubtedly the most important addition to our knowledge of the disease ever made.

*Epidemic Character.*—That the disease was infectious was suggested by the fact, recognized as early as 1881, that it occurred in epidemics. Indeed, a questionable epidemic was reported in 1841 by a Louisiana

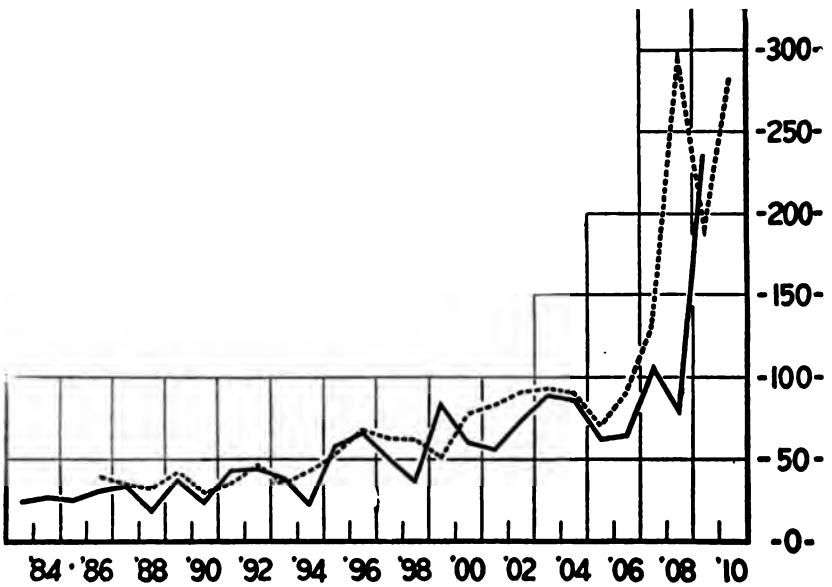



Chart 2.—Number of new patients with infantile paralysis treated at Children's Hospital, Boston, indicated by the solid black line; those treated at the New York Orthopedic Dispensary and Hospital by the dotted line; both by years.

physician. From 1881 until the present time, epidemics have been reported with increasing frequency, and since 1905 the size of epidemics has largely increased. We must remember, however, that of late greater attention has been paid to the disease and a larger number of cases has been recognized, so that the increase is in a measure apparent. Nevertheless, the increase has been too great to be accounted for by any theory of increased attention to the disease.

*Epidemic History.*—The first great epidemic of modern times occurred in Norway and Sweden in 1905, 2,000 cases being reported in Norway and Sweden together. In 1907 the first great American epidemic occurred, 2,500 cases being reported in and about New York, since which time the disease has been increasing irregularly in the United States, making a very great increase in 1910 over any previous record.

Infantile paralysis first appeared in the United States to any considerable extent in 1894, when Caverly of Rutland reported 132 cases in the

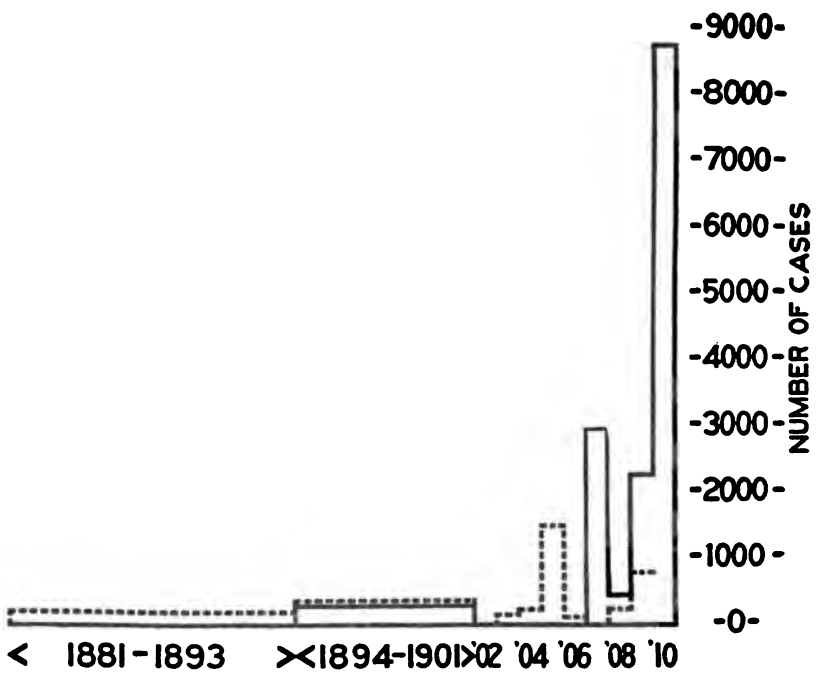



Chart 3.—Relative prevalence of infantile paralysis in the United States and Europe and Australia; the solid black line refers to the United States; the dotted line to the following countries: Italy, Sweden, Norway, Germany, Austria, France, England and Australia.

Otter Creek Valley, Vermont. Some ten small epidemics were reported in the United States during the next twelve years, and in 1907 the largest epidemic on record, that in New York, occurred, some 2,900 cases having been reported in that year. In 1908 the disease was apparently quiescent, only 392 cases being reported in the United States. This was followed

by outbreaks in 1909 in various parts of the country, and in Cuba for the first time, with a total for the year of 2,343 cases in all.

In 1910 the disease assumed much more serious proportions and was present in forty-three states. Several states had epidemics, 500 or more cases occurring in the District of Columbia, Iowa, Massachusetts, Minnesota, Indiana and Pennsylvania, and from 200 to 500 in Kansas, Maryland, New Hampshire, New York, Rhode Island, Virginia, Washington and Wisconsin (Chart 4).

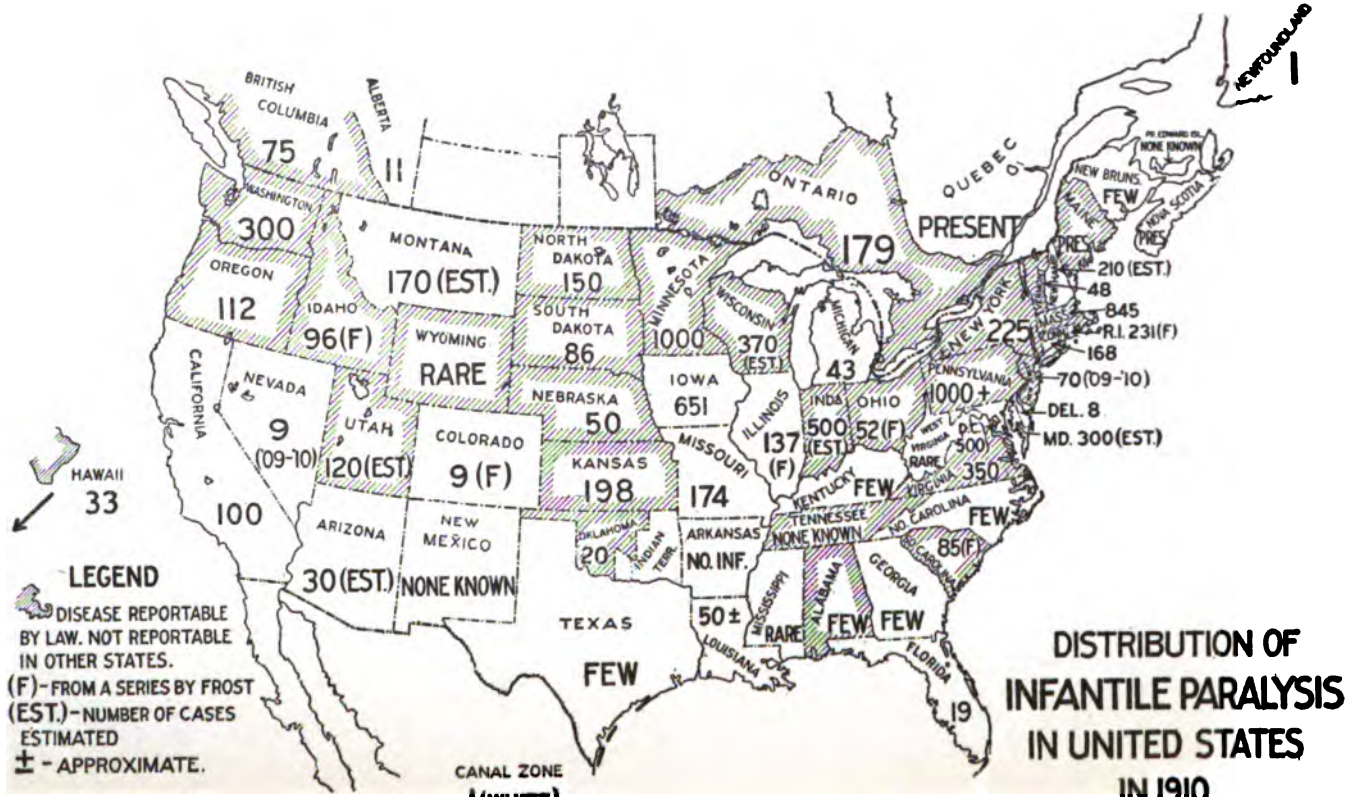
The reasons for this marked increase in the occurrence of infantile paralysis are not clear, but the certain considerations are of interest and possibly of importance.

*Question of Importation.*—No explanation has been given for the sudden increase of the disease in Norway and Sweden in 1905, but after that epidemic it seems not unreasonable to suppose that the disease may have been increased in this country by Scandinavian immigrants, who arrived to the number of about 42,000 in the year 1907. The epidemic of 1907 in New York may have had its origin in this way, and the disease may have been carried in a similar manner to the middle west, but the explanation is not wholly satisfactory, inasmuch as the outbreak of the disease in the west did not conform closely to the distribution of Scandinavian immigrants. The Massachusetts epidemic can be reasonably explained on the ground that it came from New York. In fact, the New York epidemic was sufficiently large to be a possible source for the outbreaks in various parts of this country.

*Travel.*—It has been noted in the distribution of all epidemics that they tend to spread along the lines of greatest travel; certain figures were, therefore, analyzed with regard to passenger traffic in the United States.

*Steam Railways.*—In 1904 there were 715,400,000 passengers carried by the railroads, and in 1908 there were 890,000,000, the average number of passengers per train mile being in the first period forty-six, and in the second fifty-four; that is, there were 175,000,000 more passengers carried per year in 1908 than in 1904.

*Electric Railways.*—The only available figures with regard to electric railway traffic are those for 1902 and 1907. In 1902 the number of passengers carried was 5,536,000,000, and in 1907 it was 9,500,000,000, an increase in round numbers of 4,000,000,000, or about 75 per cent. in five years.




# DISTRIBUTION OF INFANTILE PARALYSIS IN UNITED STATES IN 1910

Chart 4

*Automobiles.*—Another important factor as regards increased travel is the automobile, and here the only figures which it has been possible to analyze are those relating to Massachusetts. In 1904 there were 4,000 automobiles registered in Massachusetts; in 1909, 24,000; that is, in the five-year period the number of automobiles increased six times.

*Conclusions from Study of Travel.*—These figures show a very decided increase in travel in the United States in five years, an increase wholly out of proportion to the increase in population. It is not at all unlikely that it is one factor by which the disease has been distributed over the country; and if this conclusion is applied to the year 1894 when the Rutland epidemic occurred, the increased communication by travel becomes very much more marked by comparison.

Having considered these general aspects of the disease we now come to the closer consideration of its etiology.

## ETIOLOGY

The disease is an infectious one, caused by an ultramicroscopic virus which passes through the closest porcelain filters, its infectious character having been proved by the fact that it can be propagated in a second and many subsequent series of monkeys from tissues of a first series.

The virus is contained in the brain and spinal cord, the mucous membrane of the nasopharynx, in infected lymph-nodes, in the salivary glands, and, in the acute stage, in the cerebrospinal fluid and the blood.

The disease may be produced experimentally in monkeys by intracerebral, intraperitoneal, subdural, intraneural, perineural and subcutaneous injections, and by implantation in the anterior chamber of the eye. The disease has been caused also by the introduction of the virus into the stomach and intestines. Successful inoculation has been accomplished by rubbing the virus into a scarified or even a sound nasal membrane, and two observers succeeded in producing the disease by inhalation of an emulsion containing the virus and by implantation in the trachea. All investigators agree, however, that the intracranial route is the best for inoculation.

Inoculation of horses, calves, goats, pigs, doves, sheep, rats, cats, mice, chickens, guinea-pigs and dogs have proved negative, and monkeys have proved the most satisfactory animals for study. A paralysis may be experimentally produced in certain varieties of young rabbits and may be transmitted from one generation to another of rabbits and finally back to monkeys by successive inoculations.

The virulence of a suspension is not impaired by drying (to nine days), by freezing, nor by suspension in glycerin for five months, but it is killed by exposure to a temperature of from 45 to 50 C. in half an hour. It is also killed by such weak disinfectants as 1 per cent. solution of peroxid of hydrogen (perhydrol of Merck) by 1 to 500 solution of permanganate of potash, and by a powder containing menthol 0.5, salol 5, and boric acid 20.

The organism is not visible with the highest powers of the microscope and will not grow on the culture media in general use.

The disease in monkeys is very much like that in children, but is much more fatal; in fact, so large a proportion of inoculated monkeys die that the study of the affection clinically in them is difficult. No instances as yet have been reported in which one monkey has taken the disease from another, although long continued and intimate contact has been maintained.

The incubation period in monkeys is from five to forty-six days, with an average of eight or nine days.

### IMMUNITY

A child or animal that has once had the disease becomes apparently immune and the blood of children and monkeys recovered from the disease has been found to render other monkeys refractory to subsequent inoculation, the specific antibodies persisting in the blood for three years in one case, but being absent in another case eleven years after the onset.[1] This fact, of course, suggests that a preventive serum may be hoped for, but as yet the serum treatment is wholly in an experimental stage, and not yet ready for use in cases of the human disease.

### PERSONAL TRANSMISSION — DIRECT AND INDIRECT

In discussing the question of the transmission from patient to patient, the use of the technical and restricted term "contagious" will be avoided and the term "transmissible" will be employed.

The disease may be transmitted apparently in three ways: (1) By direct contact of a healthy child with a sick one; (2) by indirect contact by means of healthy persons passing from the sick to the well; and (3) in certain very rare instances a child has become ill shortly after occupying a house from which an affected family had moved.

1. Netter and Levaditi: Comptes rend. Soc. de biol., 1910, lxviii, 855.

*Comparative Transmissibility.*—The disease is, however, apparently less transmissible than other so-called contagious diseases with which we are more familiar.

In Minnesota a very careful investigation was conducted by Hill as to the relative transmissibility of infantile paralysis compared with that of scarlet fever, measles, etc., in the same territory. Of persons known to have been exposed to diphtheria, scarlet fever and infantile paralysis, the percentage contracting the disease was as follows: Scarlet fever, 22 per cent.; diphtheria, 17 per cent.; infantile paralysis, 6 per cent. Taking the instances of these same diseases, where one case existed in a family, the number of other cases occurring in the same family was as follows: Scarlet fever, 40 per cent.; typhoid fever, 30 per cent.; diphtheria, 29 per cent.; infantile paralysis, 17 per cent. The disease is thus apparently less transmissible than scarlet fever, typhoid fever or diphtheria.

The same evidences of mild transmissibility were shown in an investigation by Emerson, of an epidemic in the Deerfield Valley in Massachusetts in 1908, where a rural community offered excellent opportunities for study of contact. Furthermore, such instances as the following are difficult to explain by any theory of personal contact, direct or indirect:

In a sporting camp in a northern forest the 5-year old son of the proprietor had been in the camp since early spring. He had never left the camp during the summer. The camp was 5 miles from any other camp or house and 10 miles from the frontier town. There had been no other children in the camp during the summer and no illness of any kind in the guests or among animals. The few guests who were there came from the large cities, put on their hunting and fishing clothes and lived out of doors. In October the child developed a typical infantile paralysis, which still persists in one leg.

Evidence of transmission of the disease by personal contact from other epidemics is to be found in Wickman's Study, Shidler's report,[2] an epidemic observed by Frost,[3] and the Massachusetts studies.

*Possible Factors Other Than Personal Transmission.*—We come next to the consideration of the possibility of fruit, dust, insects, and animal paralysis as factors in the causation of infantile paralysis.

2. Schidler: Pediatrics, 1910, xxii, 539.
3. Frost: Public Health Bulletin 44.

*Fruit.*—As to fruit, the high cost of living has undoubtedly led to a diminished consumption of meat, and presumably to an increased consumption of fruit. Traffic in fruit has increased steadily between 1900 and 1908, the increase being from one to two million tons a year, up to 1905, since which time there has been no such sharp increase. So far as these figures go, therefore, it would not seem that any very striking factor was to be found in this analysis. Common observation would, however, seem to show that in Massachusetts, at least, there are more fruit stores and apparently more fruit in use than was the case five years ago.

*Dust.*—In order to determine the rôle of dust in the etiology of infantile paralysis, the rainfall of the country was analyzed for two periods: first, the five years from 1900 to 1904; and second, the five-year period from 1905 to 1909, when we had the greater prevalence of the disease. The total rainfall during the last five years on the Atlantic seaboard has shown everywhere a diminution, reaching a high figure in New England. On the contrary, the regions in the middle west affected by the epidemic of infantile paralysis in 1909 showed an increased rainfall during the last five years, the rainfall being as much in excess of the normal as in New England it was deficient. In the middle Atlantic states, however, including New York, the rainfall in the two periods was practically the same. Excessive dryness in the last five-year period cannot, therefore, be put down as a condition pertaining to the affected regions, if one considers New England along with Nebraska and Minnesota. But we must remember that the germ is not injured by freezing or drying, and that the season of occurrence is certainly the season of greatest occurrence of dust. Moreover, a German observer found the disease in an unduly large proportion of shoemakers' children who were much in the shops where the dried dust was flying about, and the distribution of the disease along lines of travel suggests the possibility of such a mode of transmission.

*Insects.*—There are certain facts connected with the disease which suggest the possibility of its being transmitted by insects. This matter will be dealt with in speaking of the Massachusetts studies.

It has been shown experimentally by Flexner that if flies are allowed to feed on the cord of a monkey dying of the disease that they may carry the virus for forty-eight hours.[4]

4. Flexner, Simon and Clark, Paul F.: Jour. Am. Med. Assn., June 10, 1911, p. 1717.

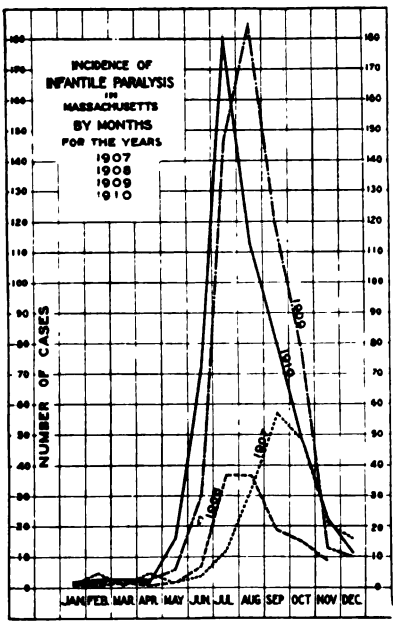
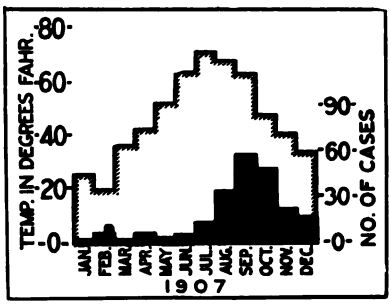



Chart 5.

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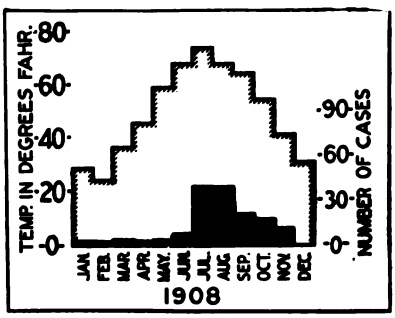


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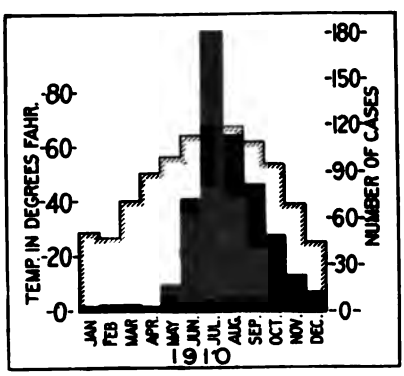


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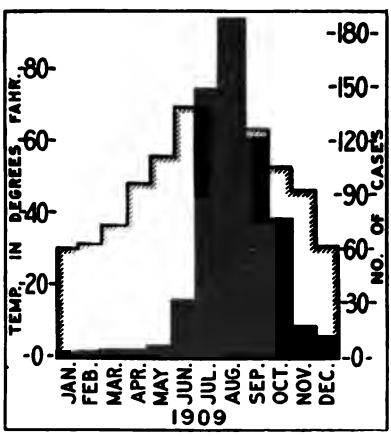


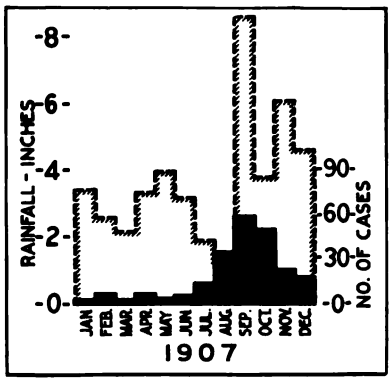

Chart 8

Chart 6.—Incidence of cases in 1907 by months shown in solid black; mean temperature in white.

Chart 7.—Incidence of cases in 1908 by months in solid black; mean temperature in white.

Chart 8.—Incidence of cases in 1909 by months in solid black; mean temperature in white.

Chart 9.—Incidence of cases in 1910 in solid black; mean temperature in white.

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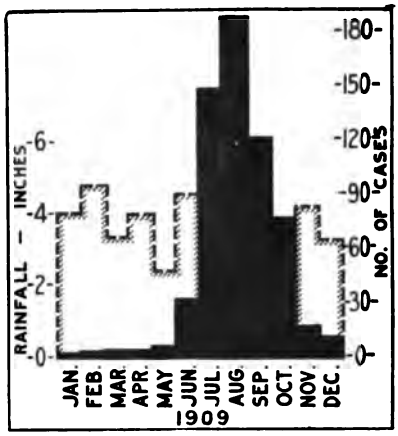


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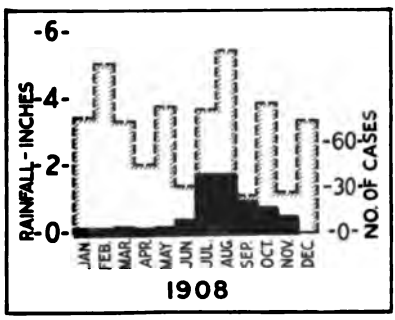


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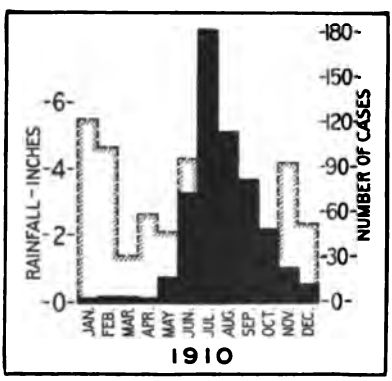


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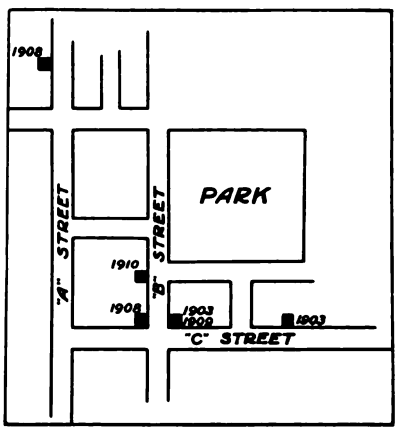


Chart 14

Chart 10.—Incidence of cases and rainfall by months in 1907. The former shown in solid black.

Chart 11.—Incidence of cases and rainfall in 1908. The former shown in solid black.

Chart 12.—Monthly incidence of cases and rainfall in 1909. The former in solid black.

Chart 13.—Monthly incidence of cases and rainfall in 1910. The former in solid black.

Chart 14.—Map showing endemic focus of infantile paralysis in a city of 119,000 inhabitants; cases occurring in the years 1903, 1908, 1909 and 1910.

*Domestic Animals.*—With regard to paralysis in the domestic animals, cases of paralysis strikingly suggestive are reported in horses, pigs, cats, dogs, rabbits, chickens, and other animals. A study of the distribution of animal paralysis in Massachusetts by means of letters addressed to veterinarians and animal inspectors showed, however, that in 1909 the distribution of cases of animal paralysis so reported did not in any way correspond to the distribution of the human disease for the same year, but much more extensive investigation along this line is necessary.

The conclusion must be that, in a consideration of etiology, infantile paralysis cannot be dismissed as a disease due only to transmission from patient to patient, but that these other factors must also be considered as possibly important.

*Season of Occurrence.*—In considering the etiology of the disease one is struck with the remarkably uniform seasonal occurrence which prevails in the north or in the tropics, in Europe or America. The disease begins to appear in the early summer, reaches its height generally in July, August or September, and diminishes through October, November and December, nearly to disappear in late winter and spring. In the southern hemisphere this behavior is reversed and the disease prevails most there in February and March, which is, of course, late summer and early fall in that locality.

*Age.*—The age of selection of the disease is between 2 and 3. Adult cases are comparatively uncommon, and occur chiefly in young adults. Dividing the ages into five-year periods, the following table was constructed by Frost:

TABLE 1.—AGE INCIDENCE IN FIVE-YEAR PERIODS EXPRESSED IN PERCENTAGES

| Age Years ..... | N. Y. Commission (729 Cases) Per cent. of Total | Lovett (Mass.) (615 Cases) Per cent of Total | Hill (Minn.) (325 Cases) Per cent. of Total |
|---|---|---|---|
| Under 1 ..... | 8.5 | 7.2 | 6.5 |
| 1 to 5 ..... | 82.0 | 64.5 | 48.6 |
| 6 to 10 ..... | 6.4 | 15.9 | 23.7 |
| 11 to 15 ..... | 1.9 | 5.0 | 7.7 |
| 16 to 20 ..... | 0.68 | 2.4 | 6.5 |
| Over 20 ..... | 0.40 | 5.0 | 7.0 |

*General Incidence.*—It affects all classes, rich and poor, in the cities and the country, in the tenements and in detached houses, on the top floor of houses, on the ground floor and in basements.

## II. PATHOLOGY, SYMPTOMS, DIAGNOSIS, PROGNOSIS, PREVENTION AND TREATMENT

*General Grouping of Symptoms and Types.*—As a working hypothesis we may keep in mind the following as to symptoms and types of paralysis:

The infection enters the body by channels as yet unknown. In some instances this infective agent causes death from general paralysis due to extensive destruction of certain spinal and cerebral centers; in a second class of cases this agent causes some permanent loss of power in part or all of one or more limbs, the back, the abdomen, or in groups of muscles supplied by cranial nerves. In a third class, the same agent causes a very local yet probably permanent paralysis in one small muscle or small group of muscles, e. g., the extensor muscles of one little finger or certain muscles of the spine.

In a fourth class, weakness or transitory paralysis ending in recovery occurs as the result of the same infection. And lastly, in a fifth class, the infective agent causes fever, prostration and perhaps pain, but does not cause sufficient destruction to bring about any paralysis or weakness.

If we recognize this descending scale in the severity of the disease as depending probably either on the dose of the poison received or on the resistance of the individual, and recognize that the involvement of the spinal centers is perhaps after all incidental rather than essential, we may well believe that the disease is far more prevalent than is generally supposed, and especially in its abortive forms.

### PATHOLOGIC ANATOMY AND HISTOLOGY

The characteristic lesions of the disease are found in the spinal cord and are most marked in the anterior horns of the gray matter of the cervical and lumbar enlargements.

In the gray matter in the early stages of the lesions are

1. Congestion of blood-vessels.
2. Edematous softening, sometimes accompanied by hemorrhage.
3. Infiltration with cells. (The cells diffusely infiltrate as well as aggregate together in foci and about the blood-vessels. They are of various kinds, but are chiefly lymphocytes and larger cells whose origin is not generally agreed on, and which are sometimes phagocytic.
4. Degeneration and diminution in the number of nerve-cells. The cytoplasm of the nerve-cell becomes hyaline and disappears leaving the

nucleus naked and necrotic, and it also eventually disappears. The degenerated cell may be surrounded and invaded by the infiltrating cells. All of the nerve-cells in a given area do not always show degenerative changes, and more of them may be involved in one side of the cord than in the other. In the later stages of the disease, in extensively affected regions, nerve-cells and their processes are absent, the tissue is disintegrated and there is infiltration with phagocytic cells, plasma cells, proliferated glia cells, and connective tissue cells. Eventually, neuroglia with some connective tissue replaces the disorganized tissue and the part may appear atrophied to the naked eye.

In the white matter in the early stages of the disease, the lesions consist of congestion, edema and cellular infiltration of the adventitial lymph spaces of the blood-vessels and to a slight extent of the white matter as well. The infiltrating cells are chiefly lymphocyte-like cells. Small foci of these cells have been noted in the white matter. In some cases, acute degenerative changes have been observd in the anterior roots.

The pia mater also shows some infiltration, chiefly with lymphocytes, which is greatest in the anterior portions of the cord in the lumbar and sacral regions.

In the spinal ganglia there may be the same infiltration as in the white matter, without marked changes in the ganglion cells.

In the later stages of the disease there is degeneration and atrophy of nerve fiber tracts, anterior roots, motor nerves and muscles, depending in extent and location on the nerve-cells which have been destroyed.

In the medulla and pons similar lesions to those in the cord are found, but the degeneration of the ganglion cells is not so extensive as in the cord.

The brain as a rule shows comparatively slight lesions. Congestion of blood-vessels, small hemorrhages, cellular infiltration of the vessel sheaths and of the brain substance in foci have been observed in various situations. In old cases, foci of sclerosis have been observed.

In acute cases, the thoracic and abdominal organs show changes which may be observed in other acute infectious diseases. A hyperplasia of the lymph-adenoid tissue of the intestine, mesentery and spleen is commonly observed in addition to acute degeneration of the myocardium, liver and kidneys, and there may be bronchopneumonia.

There is nothing in the pathologic anatomy and histology of the disease which shows the mode of entrance of the infectious agent into the body nor whether it reaches the central nervous system by the blood or by the lymph-stream.

SYMPTOMATOLOGY OF INFANTILE PARALYSIS

It is impossible in the time at our disposal to give more than the most cursory description of the symptomatology of this disease. If we think of it as a poliomyelo-encephalitis with meningeal complications and appreciate the fact that the disease may affect any or all parts of the gray matter of the central nervous system, and in all possible combinations, it is easier to understand the innumerable manifestations of the disease and it is less likely to be overlooked and mistaken for other conditions. The best classification of the various manifestations of the disease is that of Wickman, which is as follows:

1. Ordinary spinal paralysis; anterior poliomyelitis.
2. Progressive paralysis, usually ascending, less often descending; Landry's paralysis.
3. Bulbar paralysis; polio-encephalitis of pons.
4. Acute encephalitis; giving spastic mono- or hemiplegia.
5. Ataxic type.
6. Meningitic type.
7. Polyneuritic; multiple neuritic type.
8. Abortive type.

*Initial Symptoms.*—It will be well, perhaps, before taking up the special clinical types of this disease to consider briefly its initial symptoms and the possibilities of making a diagnosis before the appearance of the paralysis. There is, in the vast majority of cases, nothing characteristic about the onset. The symptoms are, in general, those of an acute infection. In many instances, however, gastro-intestinal symptoms predominate, while in others those referable to the respiratory tract are the most marked. Sweating, marked nervous irritability and general hyperesthesia are present in many instances before the onset of the paralysis, but they are not at all constant. Their presence points strongly toward this disease but their absence does not count against it. It is safe to say, therefore, that at present there is nothing about the early symptoms to justify a positive diagnosis of infantile paralysis before the onset of the paralysis, although the appearance of the symptoms of an acute infection in a child, known to have been exposed to this disease or during an epidemic, especially if accompanied by sweating, nervous irritability and general hyperesthesia, are sufficient to justify a probable diagnosis.

A leukopenia has been found in animals during the late prodromal and early part of the acute stage. It is, however, not a constant symp-

tom in man and is often replaced by a hyperleukocytosis. It is possible that there is a lymphocytosis in the early stages, but the evidence at present is not sufficient to show whether it is at all constant. It is possible that both the absolute and differential count of the leukocytes may prove useful in the early diagnosis of infantile paralysis. At present, however, they are of little or no assistance.

Experimentally, there is an increase in the number of cells in the cerebrospinal fluid during the prodromal stage, the polynuclear cells at this stage outnumbering the mononuclear. After the appearance of the paralysis, however, the mononuclear cells quickly exceed the polynuclear. A fibrin clot is also often formed during the prodromal or early part of the acute stage. The cerebrospinal fluid, in the only reported instance in which it has been examined in man during the preparalytic stage, was slightly opalescent, gave a marked protein reaction with Noguchi's test and showed an excess of polynuclear cells. The formula had begun to change to the lymphocytic, however, before the appearance of the paralysis. It seems safe to say, therefore, that in most instances a positive diagnosis of infantile paralysis can be made in the preparalytic stage by means of lumbar puncture, and that this is the only way in which a positive diagnosis can be made at this time. The value of this procedure is considerably limited, however, by the variability of the early symptoms and the consequent lack of anything to definitely suggest its use. In order to recognize the disease early, therefore, before the onset of the paralysis, it would be necessary to do a lumbar puncture on every sick child, which hardly seems a rational procedure.

*Abortive Type.*—What has been said as to the symptomatology and diagnosis of the preparalytic stage of infantile paralysis applies equally well to the abortive type (Type 8 under Wickham's classification), meaning by this term the type in which there is never any paralysis. There has been some doubt as to the existence of this type in the past, because there was no way of positively proving that the cases supposed to be of this type really were examples of this disease at all, the evidence being merely presumptive. Flexner and Clark and Frost have, however, recently demonstrated the presence of specific immune bodies in the blood of persons supposed to have had abortive attacks of infantile paralysis. The blood serum of these patients inactivated the virus of the disease, so that the infection of monkeys was impossible. There is no doubt, therefore, that abortive cases do occur. It is probable that they are as common as,

if not more common than, those with paralysis. The importance of the recognition of these cases, if the present conception as to the rôle of "carriers" in the spread of the disease is correct, is obvious.

*1. Ordinary Spinal Type.*—It hardly seems necessary to take up in detail the symptomatology of this type, with which everyone is familiar. The paralysis reaches its maximum in from a few hours to three or four days, is followed by a stationary period of from one to four weeks, which is in turn followed by a period of improvement, lasting from six months to a year, the final paralysis always being less than the initial. It is impossible to prophesy in the acute stage how extensive the final paralysis will be. In general, however, the final paralysis varies directly with the initial. The final paralysis is always flaccid; its distribution usually monoplegic or hemiplegic. In most instances some of the muscles of the paralyzed extremity escape; not infrequently only one or two are involved. The reflexes are diminished or absent, sensation is only exceptionally impaired. Deformities develop as the result of contractures of the non-paralyzed muscles.

It is not very uncommon for other muscles than those of the extremities to be involved, while these escape. Such muscles are most often the erectors of the spine and the abdominal muscles. The involvement is, moreover, not infrequently unilateral. The extensor muscles of the neck, those of one side of the spine or of one side of the abdomen may, for example, be alone involved. The deformities resulting from the paralysis or paresis of these muscles are often misunderstood and attributed to other causes.

*2. Progressive Type.*—In this type the paralysis usually appears first in the legs, and gradually extends upward. In rare instances it appears first in the arms, extends downward and finally upward to the muscles supplied by the medulla. It is probable that the great majority of the cases that have in the past been described under the term of "Landry's paralysis" really were examples of this type of infantile paralysis. When the paralysis reaches the external muscles of respiration, as it very often does, death is practically inevitable and usually occurs on the third or fourth day. The diaphragm is also sometimes involved. Death occurs sooner, of course, when this happens. This form must not be confused with that in which death results from respiratory paralysis due to involvement of the centers of respiration in the medulla.

*3. The Bulbar Type.*—Cases of this type have in the past been usually designated as polio-encephalitis superior or inferior, according to which of the cranial nerve nuclei were involved. The nuclei may be affected singly or in all possible combinations. The symptoms depend, of course, on the nuclei involved. The facial and abducens nerves are perhaps the most often affected. There may be paralysis of deglutition and of the muscles of the larynx. When the vagus is involved there are disturbances of respiration and of the cardiac action. In such instances, the respiration is often of the Cheyne-Stokes type and the prognosis is practically hopeless. Involvement of one or more of the cranial nerve nuclei is not very uncommon in connection with the ordinary spinal type of infantile paralysis. When this happens the resulting picture is a combination of the two types.

*4. Acute Encephalitic Type.*—This type was described by Strümpell many years ago under the term, "acute encephalitis of children," but it has only recently been recognized as a variety of the disease under consideration. The symptoms resemble those of acute meningitis, the deep reflexes are, as a rule, exaggerated and the paralysis is spastic. The diagnosis is usually impossible without lumbar puncture. The prognosis as to life is better than it would appear and that as to recovery from the paralysis much better than in paralysis due to other cerebral diseases.

*5. The Ataxic Type.*—Ataxia is a prominent symptom in a certain number of cases. In a few, it is the only nervous symptom; in others, it is associated with paralysis of the cranial nerves and sometimes with a small amount of spinal paralysis. The ataxia is often distinctly of the cerebellar type.

*6. The Meningitic Type.*—Symptoms of meningeal irritation are not at all uncommon in the early stags of all types of infantile paralysis. These are so marked in many instances that they present the typical picture of meningitis. Headache, rigidity of the neck and back, vomiting, tonic and clonic spasms, strabismus, Kernig's sign, delirium, coma and other signs of meningeal irritation may be present in any and all combinations. In such cases the diagnosis on the symptomatology alone is impossible before the appearance of the flaccid paralysis. Even then it is open to doubt, because flaccid paralysis is not very uncommon in meningitis, especially if it is of the tuberculous type.

A positive diagnosis can only be made in most instances by lumbar puncture. The characteristics of the cerebrospinal fluid during the pre-

paralytic stage have already been mentioned. During the acute stage it is clear, not infrequently under somewhat increased pressure, often forms a fibrin clot on standing and always contains an excess of protein and of cells. The cells are chiefly of the mononuclear type, most of them being lymphocytes. These characteristics are, however, the same as those found in tuberculous meningitis, the type of meningitis with which infantile paralysis is most likely to be confused. A positive diagnosis between them can only be made, therefore, by the examination of the cerebrospinal fluid for tubercle bacilli. The characteristics of the cerebrospinal fluid in meningococcal, influenzal and pneumococcal meningitis are so different from those in infantile paralysis that no confusion with these conditions is possible.

*The Polyneuritic Type.*—Pain is a prominent symptom in many instances. It is sometimes located in the joints, but is more often along nerve-trunks or indefinite in its distribution. It is usually most marked in the paralyzed parts. There is occasionally tenderness over the nerve-trunks. The pain and tenderness are sometimes marked enough to cause the paralysis to be entirely overlooked and a diagnosis of rheumatism or scurvy to be made.

The extremities are often held rigidly and all motion as vigorously resisted as possible, because of the pain on motion. This combination of rigidity and resistance is possible, of course, only when the muscles are partially paralyzed or when some of them are intact. The failure to appreciate the significance of this combination of flaccidity and spasticity not infrequently leads to errors in diagnosis during the acute stage.

### PREVENTION

The question of the prevention of the disease is of great importance, and you are probably asked as frequently as we are in Massachusetts: "What shall I do to protect my children from the disease?" — a question which we must answer fairly with due regard to the interests of the patient, remembering, however, that advice too radical will increase the panic which is sure to appear in a locality where the disease is prevalent. It seems proper to advise people with children that, other things being equal, it is wise not to go for the summer to a locality where the disease is known to be prevalent. If, however, people find themselves in such a locality, the children and members of the family should keep away from other children who are in the acute stage of paralysis, and from children who are sick with other indefinite ailments.

In such localities it would seem wise to keep children away from children's entertainments, circuses and electric cars, and to prohibit playing with sick or paralyzed domestic animals.

*Length of Quarantine.*—We have at present no data as to how long the infectious period of the acute stage lasts, and any attempt to determine the length of quarantine must be mere guesswork.

With regard to the necessary length of quarantine, general consent has placed it at from two to four weeks. The recent experiments of Osgood and Lucas in this matter are, however, important inasmuch as they found an active virus in the nasopharyngeal mucous membrane of a paralyzed monkey, five and one-half months after the active stage of the disease had passed. The virus disappears from the nervous system in three or four weeks, or less, according to Flexner's experiments.

### MORTALITY

The death-rate is about seven or eight per hundred, as the disease has existed in Massachusetts, but no foreign statistics show as low a figure as this, being from 10 to 22 per cent. In persons older than 10, the mortality-rate is higher than between 1 and 10, and under 1 year the disease seems more fatal.

The mortality table is interesting as showing the difference between the foreign and American death-rate.

TABLE 2.—COMPARISON OF FOREIGN AND AMERICAN DEATH-RATE

| | Year | Cases | Death | Mortality Per cent. |
|---|---|---|---|---|
| Caverly, Vermont | 1894 | 132 | 18 | 14.5 |
| Wickman, Sweden | 1905 | 868 | 145 | 16.7 |
| Leegaard, Norway | 1905 | 577 | 84 | 14.5 |
| Zappert, Austria | 1908 | 266 | 29 | 10.8 |
| Lindner and Mally, Austria | 1908 | 71 | 16 | 22.5 |
| Furntrat, Steiermark | 1908 | 433 | 57 | 13.1 |
| Krause, Germany | 1909 | 633 | 78 | 12.3 |
| Muller, Germany | 1909 | 100 | 16 | 16.0 |
| Peiper, Germany | 1909 | 51 | 6 | 11.7 |
| Eichelberg, Germany | 1909 | 34 | 7 | 20.6 |
| Mass., U. S. A. | 1907-1910 | 1,599 | 125 | 7.9 |

The mortality of cases in older children and in adults is higher than in other classes.

TABLE 3.—SHOWING HIGHER MORTALITY IN THE MORE ADVANCED AGES

| | Age .... | Mortality, Per cent. |
|---|---|---|
| Wickman | 12 to 32 | 27.6 |
| Leegaard | 15 to 30 | 25.8 |
| Furntrat | Over 15 | 25.5 |
| Lindner and Mally | Over 11 | 50.0 |
| Mass., 1910 | Over 10 | 20.0 |

PROGNOSIS

A few years ago it was supposed by most persons that practically all patients once paralyzed were to some extent paralyzed for life. But more careful study has shown us a better and more encouraging state of affairs. In the cases in Massachusetts, in 1909, a group of 150 occurring near Boston were studied in detail and it was reported that twenty-five, or 16.7 per cent., had wholly recovered inside of three months. This statement was not believed and the investigators were sent back to review their work. Each one of the children was stripped and the movements of ankle. knee, hip, shoulder, elbow, wrist and spine were examined. The statement can be definitely made, therefore, that, of this group, 16 per cent. had wholly recovered within three months.

The commonest type of final paralysis is an affection of one leg varying in degree from a slight limp in walking to a condition which requires the use of a brace; if both legs are involved, crutches are occasionally also required.

In short, a disability from infantile paralysis so great as to prevent an adult from earning his or her own living, occurs in a very small number of patients properly treated, but the ultimate condition of neglected cases is frequently distressing.

In connection with the question of treatment it is important to consider the reasons for this tendency to recovery, which are to be found in the pathology of the disease.

At the height of the disease there is an extensive perivascular infiltration of the blood-vessels of the cord, diminishing their lumen and inducing anemia and edema of the regions of the cord supplied by them. In addition to which there is also inflammatory edema of the nerve-tracts in the white matter and edema of the nerve-cells in addition to any destructive process which may be going on in neighboring cells. These changes, of course, cause loss of function in the parts affected, expressed as a temporary paralysis which passes away as the perivascular infiltration

subsides. This apparently accounts for the improvement of paralysis in the early stage of the disease which exists in all non-fatal cases.

But the spontaneous improvement in the paralysis of the early history of the disease is no more important than improvement to be obtained by proper treatment in the chronic stage of the disease, after there is every reason to believe that the temporary perivascular infiltration has subsided, and the reason for this later improvement apparently rests on another pathologic basis. Assuming that the phenomena just described have ended, but that permanent destruction of certain motor centers in the spine has occurred, leaving a definite motor paralysis, the question arises, What reason is there to look for improvement in this? The answer apparently is as follows:

The spinal motor centers are grouped in cigar-shaped bundles whose length lies in the long axis of the spine. At each level of the spine are several of these bundles which overlap each other and communicate freely. Each bundle furnishes impulses to more than one muscle and each muscle receives impulses from more than one bundle. The blood-supply of the spine comes in horizontally and the lesions of this disease are most marked around the vessels. The distribution of the destructive process is therefore likely to be horizontal, while the distribution of the motor bundles is longitudinal. For this reason it is likely that if the destruction has not been too extensive, certain parts of the motor bundles will have escaped, leaving certain cells in some of them capable of function but which, in order to perform function, must acquire new connections and new groupings.

For this reason it will be seen, as will be maintained later, on the ground of practical experience, that muscle-training offers the best hope of the restoration of power to affected muscles in the chronic stage of the paralysis. It is an attempt to bring motor impulses from the brain down to the affected centers in the cord, there to establish new connections and new routes to the paralyzed muscles. The more impulses of this sort, however feeble they may be at first, to reach the affected muscles the better the chance of establishing finally routes which may serve for the transmission of impulses strong enough to secure efficient muscular contraction.

### TREATMENT — ACUTE STAGE

In the matter of treatment much progress has been made in the last four years. In the acute stage meddlesome and useless treatment by

stimulating drugs and counter-irritants has become largely discredited. Rest is very important, although cathartics and hexamethylenamin are of probable value, the latter drug being used with the object of setting free formaldehyd in the cerebrospinal fluid. Indeed, it has been shown experimentally that if hexamethylenamin is administered by mouth to monkeys, and if such animals are subsequently inoculated either subdurally or by the intracerebral route, paralysis is, in a certain proportion of cases, delayed or prevented. The value of the drug, therefore, in the prevention of infection would seem to be indicated, but there is as yet no experimental evidence to show that the drug is of much use after the disease has once begun.

In view of the pathologic condition, it is simply common sense to keep the patient recumbent and quiet and to avoid irritation of the muscles supplied by the affected nerve-centers. Massage and electricity should not, therefore, be used until there is reason to believe that subsidence of the inflammation has taken place. We may probably interpret the tenderness of the limbs as showing, while it lasts, the persistence of some degree of spinal or neural inflammation and until that has wholly disappeared we are not justified in the use of passive movements, massage or electricity.

Some men of large experience discourage all active treatment before the expiration of six weeks at least, but excellent results are frequently obtained by beginning treatment earlier on cases characterized by slight and transient tenderness. We should, however, discourage all active treatment until tenderness has wholly disappeared.

Another point of primary importance in early treatment is the prevention of contractures and deformities due to unopposed muscular action. Except in paralysis of the back and shoulder these contractures and deformities are always preventable, the contracture of the tendo Achillis, e. g., which is so frequent and so troublesome, being easily prevented by the use of splints supporting the foot at a right angle.

We read much concerning the relative merits of electricity and massage in the restoration of muscular power, but who shall pronounce as to the value of either in an affection in which paralysis varies so much in extent and severity and the recovery from which is so surprisingly different, irrespective of methods of treatment? Both methods have as an object the stimulation of muscular fibers and the maintenance of muscular nutrition, but both are inferior to muscular training in active

treatment. This method of treatment is most useful in connection with massage or electricity and aims to cultivate the transmission of a voluntary motor impulse from the brain, down the cord to the paralyzed, weakened or stretched muscles. A flicker of motion, in an affected muscle, is often the forerunner of a return of some degree of power, and assistance by the hand in performing voluntary movements of the foot, for example, is often of great use.

*Apparatus.*—As to the use of apparatus, when a child in attempting to stand cannot, for example, hold the knee extended in weight-bearing, or when he stands in a position of deformity, for instance, with flat foot, apparatus should be applied to restore normal relations. Nothing but harm can result from sitting or going about with a curved spine, a hyperextended knee, or a foot rolled over on its inner or outer border. Stretching of muscles and ligaments and permanent bony deformities which are sure to result are worse than the use of braces, objectionable as the latter are.

Contractures which exist in neglected cases are not extremely resistant early in their history and must be removed before satisfactory mechanical treatment can be carried out. Most of them can be removed if stretched by means of bed traction or by the use of a series of correcting plaster bandages or by cutting. Operative treatment, except for the minor tenotomies, should not be undertaken for two years after the attack and preferably not then in children under 10.

*Surgical Treatment.—Operation.*—Tendon transplantation is a most useful measure and now that it has passed through its period of extravagant claims and unjustified condemnation, it may be said, in properly selected cases and with proper technic, to produce generally satisfactory and often brilliant results.

It consists in transplanting the distal end of a healthy muscle to the periosteal insertion of a paralyzed one, the foot or knee or arm being thus rebalanced. Since we have learned to prolong tendons by silk, the range and application of the operation has increased. We plan our operation, dissect and cut off our good muscle and if it is too short lengthen it at its distal end by heavy silk, we then insert it where we like, a new and sound tendon forming around the silk. In this way peroneals may replace tibials at the ankle or *vice versa,* hamstrings may be carried forward and inserted into the tibia to serve as knee extensors when the quadriceps is paralyzed and the trapezius may be substituted at the shoulder for a paralyzed deltoid.

*Arthrodesis.*—As a means of stiffening and making stable useless joints, arthrodesis has been found a useful measure. This operation consists in opening such joints and removing enough cartilage to secure ankylosis, and is applicable to the hip, ankle, elbow, and shoulder in children over 12, and to the knee in adults but not to the knee in growing children.

*Silk Ligaments.*—For the correction of foot drop in paralyzed legs we have made use more and more of anterior silk ligaments, the idea being to prevent plantar flexion of the foot but still to allow dorsal flexion. Heavy strands of silk are sewed into the anterior surface of the tibia, carried down under the annular ligament of the ankle and sewed into the dorsal surface of one of the tarsal bones. This operation is distinctly preferable to arthrodesis.

Nerve transplantation has not yet emerged from its experimental stage.

Finally, one of the most important things that orthopedic surgeons have learned of late years is that the hope for improvement in these cases through efficient and suitable treatment need not be given up in six months or one year or ten years, but that the possibility of improvement seems to persist almost indefinitely.

### III. INFANTILE PARALYSIS AS OBSERVED IN MASSACHUSETTS, 1907-1910

The investigation of infantile paralysis in the state of Massachusetts by the State Board of Health for the four years, 1907 to 1910, inclusive, shows that during that period 2,138 cases of the disease were reported to the office of the State Board of Health. These cases were distributed by years as follows:

| | |
|---|---|
| 1907 | 234 |
| 1908 | 136 |
| 1909 | 923 |
| 1910 | 845 |

It is apparent from these figures that the disease in Massachusetts has, in a general way, during the period mentioned, increased in frequency, and it has been shown that a larger number of towns were infected each year.

*Two-Year Periodicity.*—There is, moreover, in these figures a suggestion of what may be an important phenomenon, and that is the appearance of a two-year periodicity for this disease. This phenomenon is

noticeable in the distribution in general. In 1905 occurred the great Scandinavian epidemic. In 1906 there were no important epidemics. In 1907 occurred the New York epidemic. In 1908 there were only a few small epidemics and none of importance reported in Europe. In 1909 occurred the Massachusetts, Minnesota and Nebraska epidemics, two large and one small German epidemics, a large outbreak in Austria and the epidemic in Cuba. In 1910 from Europe no large epidemics were reported so far as we have been able to learn. The occurrence of the disease in this country in 1910 has already been dealt with.

This two-year periodicity has been noted a number of times in our investigation; for instance, in 1907 the western part of the state was quite sharply affected with infantile paralysis, whereas in 1908 the disease was almost non-existent in that same region. Again in 1909 the disease cropped up, but in 1910 hardly any evidence of infantile paralysis was noted in that neighborhood. In 1908, furthermore, in the Turners Falls district, etc., a very marked epidemic occurred, involving sixty-nine cases in a quite sharply circumscribed locality. In 1909 but one case occurred in this whole region. So that one can prophesy, to a certain extent, at least, that a limited locality, severely affected during one year, will probably enjoy partial immunity in the succeeding year. On the other hand, many localities having the disease to a moderate extent seem to go on from year to year at about the same rate.

*Relative Prevalence in Smaller Cities and Towns.*—Infantile paralysis is a disease affecting by preference the smaller cities and towns. This statement rests on the observation of 2,138 cases in Massachusetts, which have been analyzed in this regard.

The incidence per 1,000 of the population was recorded for every affected city and town in the state for four years. For each year the cities and towns were then arranged in the order of greatest incidence and then the first twenty-five on the list were contrasted with the last twenty-five for each year.

The average population for the first twenty-five was then reckoned for the four years and proved to be 5,205. The average population of the last twenty-five on the list, those where the incidence was least, was 52,674. A further study of the table shows that some such proportion as this existed in every one of the four years. That is to say, cities and towns where the disease was relatively least frequent were ten times as large on the average as those where it was most frequent. Furthermore, as a

control, we tabulated the cases of scarlet fever reported in the state for the year 1910 in the same way. In the twenty-five cities and towns in which scarlet fever was most prevalent the average population was 6,446, and in the twenty-five where it was least prevalent per 1,000 of the population the average population was 7,633, practically the same, showing that scarlet fever showed no such predilection for the smaller cities and towns (Table 4).

TABLE 4.—COMPARATIVE PREVALENCE OF INFANTILE PARALYSIS AND SCARLET FEVER WITH REFERENCE TO POPULATION OF CITIES

| Disease<br>.....<br>.....<br>..... | Twenty-five Cities Where Disease was *Most* Prevalent | Twenty-five Cities Where Disease was *Least* Prevalent |
|---|---|---|
| Acute epidemic poliomyelitis ..... | 5,205 | 52,674 |
| Scarlet fever ..... | 6,446 | 7,633 |

In seeking to analyze some of the conditions which were constant in the smaller cities and towns which did not prevail in the larger, the number of domestic animals in each city and town was looked into and the analysis contributes the information that the number of such animals is relatively very much greater in the smaller cities and towns than in the larger. Such a fact may have no significance whatever, or it may in the future prove of importance (Table 5).

TABLE 5.—PREVALENCE OF INFANTILE PARALYSIS WITH REFERENCE TO THE NUMBER OF ANIMALS IN CITIES AND TOWNS

| Total Number of Animals Assessed in Twenty-five Cities and Towns where the Disease was *Least* Prevalent, i. e., in the Larger Cities and Towns. | | Total Number of Animals Assessed in the Twenty-five Cities and Towns where the Disease was *Most* Prevalent, i. e. in the smaller Cities and Towns. | |
|---|---|---|---|
| Total population ..... | 943,614 | Total population ..... | 142,639 |
| Total number of cows ..... | 11,160 | Total number of cows..... | 12,801 |
| 1 cow to 84.5 inhabitants. | | 1 cow to 11 inhabitants. | |
| Total number of horses .... | 29,519 | Total number of horses.... | 10,352 |
| 1 horse to 32 inhabitants. | | 1 horse to 14 inhabitants. | |
| Total number of swine .... | 3,288 | Total number of swine..... | 2,374 |
| 1 swine to 287 inhabitants. | | 1 swine to 60.5 inhabitants. | |
| Total number of fowls..... | 41,887 | Total number of fowls..... | 79,797 |
| 1 fowl to 22.5 inhabitants. | | 1 fowl to 1.75 inhabitants. | |
| Total number of dogs..... | 23,854 | Total number of dogs..... | 5,865 |
| 1 dog to 39.5 inhabitants. | | 1 dog to 24.3 inhabitants. | |

Of course, this is only one of many conditions which are different in the two classes but the persistence year after year of this greater preva-

lence of the disease in the smaller cities and towns must mean something with regard to the etiology of the disease if we were only able to interpret it.

*Seasonal Occurrence.*—The occurrence of the disease by months shows that the maximum incidence of infantile paralysis occurs between June and November. In 1907 the largest number of cases occurred in September. In 1908 July and August had equal numbers; 1909 had the largest number in August, and 1910 in July. There seems thus to be in Massachusetts a distinct tendency of the maximum incidence to recede in point of time, a phenomenon which should it occur in 1911, might be worthy of serious investigation (see Charts 5, 6, 7, 8 and 9).

*Age.*—The combined experience of three years, 1908 to 1910, shows that 6.13 per cent. of the cases occurred before the end of the first year; 66.94 per cent. before the end of the fifth year, and 83.1 per cent. before the end of the tenth year. Moreover, the Massachusetts figures give the impression that the disease is more frequent in adults than has been commonly supposed (Table 6).

TABLE 6.—OCCURRENCE BY AGE PERIODS (1908-1910) PARESIS

| Age, Years | Cases | Per cent. |
|---|---|---|
| Birth to 12 mos., inc. | 55 | 6.13 |
| 1 | 119 | 13.26 |
| 2 | 155 | 17.35 |
| 3 | 125 | 13.93 |
| 4 | 92 | 10.25 |
| 5 | 54 | 6.02 |
| | 600 | 65.94 |
| 6 to 10, inc. | 145 | 16.16 |
| | 745 | 83.10 |
| 11 to 20, inc. | 83 | 9.25 |
| | 828 | 92.3 |
| 21 to 30, inc. | 39 | 4.34 |
| 31 to 72, inc. | 17 | 1.89 |
| Not stated | 13 | ..... |
| | 897 | ..... |

*Sex.*—As far as sex is concerned, the relative incidence is expressed by the figures of 56 per cent. for males and 44 per cent. for females, as reported for the four years, 1907 to 1910 (Table 7).

| TABLE 7.—SEX (1907-1910 | | Per cent. |
|---|---|---|
| Males | 906 | 56.66 |
| Females | 689 | 43.08 |
| Not stated | 4 | 0.25 |
| Total | 1,599 | ..... |

*Mortality.*—The mortality under 1 year is high, being for 1909-10 12.19 per cent. Between 1 and 10 years the fatality seems to drop, being 6.24 per cent., but after ten years the mortality again rises and reaches 14.81 per cent. The average mortality is 7.9 per cent. (Table 8).

TABLE 8.—MORTALITY BY AGE (1909-1910)

| Age, Years | Cases | Deaths | Mortality, Per cent. |
|---|---|---|---|
| Under 1 | 82 | 10 | 12.19 |
| 1 to 10 | 945 | 59 | 6.24 |
| Over 10 | 189 | 28 | 14.81 |
| Totals | 1,216 | 97 | ..... |
| Average mortality | | | 7.9 |

*Environment of Patients.*—As regards the character of the house, practically an equal number of cases occurred in detached houses, in tenements or in apartments. Furthermore, there seemed to be no marked predilection of the disease for any special floor of the house. The house was said to be dry in 72 per cent., damp in 27 per cent., and medium in 1 per cent. No apparent relation to moisture can, therefore, be made out. The sanitary conditions were either excellent, good or fair in 85.6 per cent. cases, and bad in only 11.5 per cent. The age of the house was not remarkable. 41.14 per cent. of patients living in new houses; that is to say, within the first and tenth year of its existence; whereas 58.85 per cent. lived in houses more than ten years old.

It has seemed at times as if the disease preferred river beds, but this factor in the occurrence of the disease must rest on other basis than mere propinquity, because, although thirty-three patients are said to have lived near a river or near water, 317 lived more than one-eighth of a mile from any stream, pond, or beach, so that it seems probable that any marked occurrence of the disease along the water courses is due to other factors than a neighborhood of water, the determining influence being in all probability increased personal contact due to the fact that all highroads, electric railways and railroads are very apt to follow river valleys, and cities and towns are, therefore, more likely also to be situated along such water courses.

In the same way, no especial relation could be found between the occurrence of infantile paralysis and nearness to railroads. The experience of Wickman, as shown by his maps, certainly seemed to show a distinct preference of the disease for localities near railroads, but in Massachusetts we have not been able to observe any etiologic connection between the two. In 1909-10, 30.56 per cent. of the cases occurred within one-eighth of a mile of the tracks, while 69.42 per cent. were more than one-fourth of a mile away.

A study of sewage condition shows that the disease occurs under all conditions of sewage disposal and as regards water supplies from metropolitan and city systems, as well as from wells and springs (Tables 9, 10, 11, 12, 13, 14, 15, 16 and 17).

TABLE 9.—CHARACTER OF HOUSE (1907-1909)

| | | Per cent. |
|---|---|---|
| Detached | 220 | 49.54 |
| Tenements | 224 | 50.45 |
| Total | 444 | ..... |

TABLE 10.—FLOOR OF HOUSE INHABITED BY FAMILY (1907 AND 1909)

| | | Per cent. |
|---|---|---|
| The whole house | 75 | 21.06 |
| The first floor | 139 | 39.04 |
| First floor and basement | 3 | .84 |
| Second floor | 101 | 28.37 |
| Third floor | 32 | 8.98 |
| Upper stories | 6 | 1.68 |
| Total | 356 | ..... |

TABLE 11.—LOCATION OF HOUSE (1907-1910)

| | | Per cent. |
|---|---|---|
| Dry | 459 | 71.38 |
| Damp | 177 | 27.52 |
| Medium | 7 | 1.08 |
| Total | 643 | ..... |

TABLE 12.—SANITARY CONDITION (1907-1910)

| | | Per cent. |
|---|---|---|
| Excellent | 123 | 18.83 |
| Good | 271 | 41.50 |
| Fair | 165 | 25.25 |
| Bad | 74 | 11.33 |
| Not stated | 20 | 3.06 |
| Total | 653 | ..... |

TABLE 13.—AGE OF HOUSE (1909-1910)

| | | Per cent. |
|---|---|---|
| New House (1-10 yrs.) | 144 | 41.14 |
| Old House (over 10 yrs.) | 206 | 58.85 |
| Total | 350 | ..... |

TABLE 14.—NEARNESS OF HOUSE TO WATER (STREAM, POND OR BEACH) (1909-1910)

| | | Per cent. |
|---|---|---|
| On river | 33 | 9.42 |
| Within ⅛ mile | 66 | 18.85 |
| Within ¼ mile | 89 | 25.42 |
| Within ½ mile | 78 | 22.28 |
| Within 1 mile | 84 | 24.00 |
| Total | 350 | ..... |

TABLE 15.—NEARNESS OF HOUSE TO RAILROAD (1909-1910)

| | | Per cent. |
|---|---|---|
| On railroad | 57 | 16.28 |
| Within ⅛ mile | 50 | 14.28 |
| Within ¼ mile | 44 | 12.57 |
| Within ½ mile | 114 | 32.57 |
| Within 1 mile | 85 | 24.28 |
| Total | 350 | ..... |

TABLE 16.—CHARACTER OF SEWAGE DISPOSAL (1908-1910)

| | | Per cent. |
|---|---|---|
| Sewage (Met.) | 110 | 26.25 |
| Sewage (City, etc.) | 211 | 50.35 |
| Cesspool | 23 | 5.48 |
| Vault | 60 | 14.31 |
| Privy | 15 | 3.57 |
| Total | 419 | ..... |

TABLE 17.—CHARACTER OF WATER-SUPPLY (1908-1910)

| | | Per cent. |
|---|---|---|
| Metropolitan | 120 | 27.98 |
| Town | 62 | 14.45 |
| City | 172 | 40.09 |
| Well | 17 | 3.96 |
| Spring | 58 | 13.51 |
| Total | 429 | ..... |

*Rainfall.*—The deficiency in rainfall during the last eight years has been, of course, very marked, and this factor may be of importance in the spread of the disease. It certainly has to be taken very seriously into

consideration if we accept the suggestion of Hill of Minnesota that dust, especially dust infected with horse manure, may be responstible for the transference of this disease. The deficiency of rainfall in Massachusetts has varied since 1904, when it was 1.35 inches, to 9.42 inches in 1910. With the deficiency of rainfall during each year of this period has occurred a sort of cumulative effect, which makes this deficiency relatively more important each year. A study of the deficiency of rainfall shows that the largest number of cases have not occurred in the driest years in Massachusetts (Table 18 and Charts 10, 11, 12, 13).

TABLE 18.—DEFICIENCY RAINFALL (1904-1910)

| Year | Cases in State | Actual | Normal | Deficiency |
|---|---|---|---|---|
| 1904 | ... | 43.81 | 45.16 | — 1.35 |
| 1905 | ... | 37.60 | ..... | — 7.56 |
| 1906 | ... | 43.21 | ..... | — 1.95 |
| 1907 | 234 | 44.49 | ..... | — 0.67 |
| 1908 | 136 | 37.61 | ..... | — 7.55 |
| 1909 | 923 | 42.10 | ..... | — 3.06 |
| 1910 | 845 | 35.50 | ..... | — 9.42 |
| | | | | —31.56 |

*Dust.*—A study of the amount of dust in affected localities shows a report of a moderate amount in more than half of the cases while in 36 per cent. of the total number much dust or an excessive amount was reported. The matter is not, however, one capable of measurement or exact determination and the table cannot be regarded as important (Table 19).

TABLE 19.—RELATION TO DUST (1909-1910)

| | | Per cent. |
|---|---|---|
| No dust | 0 | ..... |
| Very little dust | 29 | 8.28 |
| Moderate amount of dust | 195 | 55.71 |
| Much dust | 118 | 33.71 |
| Excessive amount of dust | 8 | 2.28 |
| Total | 350 | ..... |

*Insects, Etc.*—The possible transfer of the disease by vermin, insects, rodents, etc., was investigated, but the figures are not at all conclusive, and very little knowledge of value is likely to come in this department of the work, until individual infected localities are investigated by persons expert in the study of entomology, a line of investigation of the greatest importance (Table 20).

TABLE 20.—PRESENCE OF VERMIN, INSECTS, RODENTS, ETC. (1909-1910)*

| | | Per cent. |
|---|---|---|
| Flies | 298 | 90.85 |
| Mosquitoes | 142 | 43.29 |
| Mice (house) | 123 | 37.5 |
| Ants | 97 | 29.57 |
| Rats | 77 | 23.47 |
| Bedbugs | 70 | 21.34 |
| Roaches | 64 | 19.51 |
| Spiders | 54 | 16.46 |
| Mice (field) | 24 | 7.31 |
| Biting flies | 10 | 3.04 |
| Fleas | 4 | 1.21 |
| Grubs and Caterpillar | 3 | .91 |
| Bees | 2 | .609 |
| Sand fleas | 1 | .304 |
| Snakes | 1 | .304 |
| Crickets | 1 | .304 |
| Squirrel | 1 | .304 |
| Leeches | 1 | .304 |
| Brown tail moths | 1 | .304 |
| Moles | 1 | .304 |
| Total | 328 families | |

*Report 1907 and 1908 only for flies and mosquitoes.

*Domestic Animals.*—The rôle played by domestic animals in the transfer of the disease is one of great possible interest, but as yet the interrelation of the paralyses of man with those of animals has not been sufficiently marked to justify any definite conclusion. Many cases of paralysis in animals have been reported, but the instances in which paralysis in human beings has been coincident with such animal paralysis have been rare (Table 21).

TABLE 21.—DATA AS TO DOMESTIC ANIMALS (1909-1910)

| | | Per cent. |
|---|---|---|
| No animals of any kind in | 131 | 39.93 |
| Animals in | 197 | 60.06 |
| 125 animals had sickness, paralysis or death in | 70 | 21.34 |
| Total | 328 families | |

*Transmissibility.*—The degree of contagiousness of infantile paralysis is a question of great theoretic and practical importance. It is one which at the present time it is practically impossible to analyze exactly because, associated with the paralytic cases of this disease, occur an unknown number of so-called abortive cases which may be of the greatest importance in transferring to others paralytic types of the affection. Furthermore,

these unknown abortive cases become immune to subsequent infection, and if included in any study of comparative contagiousness, will go far, undoubtedly, to vitiate any conclusions drawn. Our figures show that in 350 cases carefully studied, there was direct contact with an acute case in 13 per cent.; direct contact with possible abortive cases in 1.42 per cent.; with chronic cases in 4.28 per cent.; and that there was, undoubtedly, indirect contact with an acute case through a third person in 4 per cent. of the cases (Tables 22 and 23. See Chart 14 for an endemic focus in a city of 119,000 inhabitants).

TABLE 22.—INSTANCES OF CONTAGIOUSNESS (1909-1910)

| Certain direct contact: | | Per cent. |
|---|---|---|
| With acute case | 46 | 13.14 |
| With possible abortive case | 5 | 1.42 |
| With chronic case | 15 | 4.28 |
| With both acute and chronic cases | 2 | .57 |
| Certain indirect contact with acute case by third person | 14 | 4.00 |
| Number of cases investigated | 350 | ..... |

TABLE 23.—FAMILIES WITH MORE THAN ONE CASE (REASON FOR SUSPECTING CONTAGION) 1908-1910

| | | Per cent. |
|---|---|---|
| One case | 357 | 92.24 |
| Two cases | 27 | 6.97 |
| Three cases | 3 | .77 |
| Total | 387 | ..... |

*Institution Cases.*—Forty-four institutions for children in Massachusetts were written to in 1910, in order to ascertain whether or not any cases of acute epidemic poliomyelitis had originated within those institutions during the year. One institution, containing 360 children, in Fall River, reported a single case, a boy, 4 years old. No secondary cases occurred in this institution (Table 24).

| TABLE 24.—INSTITUTION CASES | Cases | Incidence per 1,000 |
|---|---|---|
| 44 institutions with 3,600 children under 15 years of age | 1 | .277 |
| Mass., with a population of 851,092 children under 15 years (Census of 1905) showed in 1910 cases of acute epidemic poliomyelitis under 15 years | 532 | .625 |

Children in institutions therefore would seem to be, in some measure and in some way as yet unexplained, protected from this disease. Their opportunities for contact with the outside world are obviously much cur-

tailed in comparison with those of the ordinary child, and therein lies very probably the reason for their immunity.

TABLE 25.—SWIMMING, WADING OR PADDLING (1908-1910)*

| | | Per cent. |
|---|---|---|
| Swimming, wading or paddling | 105 | 25.05 |
| No such history | 314 | 74.94 |
| Total | 419 | ..... |

*Water contaminated more or less in every instance.

TABLE 26.—ACCIDENT, OVER-EXERTION OR FALL PRECEDING ATTACK (1907-1910)

| | | Per cent. |
|---|---|---|
| Accident | 41 | 8.97 |
| Over-exertion | 47 | 10.28 |
| Fall | 67 | 14.66 |
| No such history | 302 | 66.08 |
| Total | 457 | ..... |

TABLE 27.—DISEASES PREVALENT IN TOWN AT TIME OF OCCURRENCE OF INFANTILE PARALYSIS (1909-1910)

| | Cases | Per cent. |
|---|---|---|
| Not known | 159 | 46.49 |
| Infantile paralysis | 120 | 35.08 |
| Whooping cough | 12 | 3.508 |
| Measles | 11 | 3.21 |
| Gastro-enteritis | 8 | 2.33 |
| Diarrhea | 6 | 1.75 |
| Influenza | 6 | 1.75 |
| Tonsillitis | 4 | 1.16 |
| "Rheumatic fever" | 4 | 1.16 |
| Scarlet fever | 3 | .87 |
| Mumps | 2 | .58 |
| Malaria | 2 | .58 |
| Pneumonia | 1 | .29 |
| Coryza | 1 | .29 |
| Chicken pox | 1 | .29 |
| Typhoid | 1 | .29 |
| Diphtheria | 1 | .29 |
| Total | 342 | ..... |

*Swimming, Etc.*—Just prior to the disease, there was a history of swimming, wading, or paddling, in water more or less contaminated, in 25 per cent. of the cases just before attack (Table 25).

*Accidents.*—In the same way, 34 per cent. of 457 cases gave a history of accidents, over-exertion or falls. With regard to the swimming, etc., the percentage would seem no higher than one would expect in any group

of children at this season, living near the water. But the percentage of thirty-four accidents, falls and over-exertion just before the attack would seem perhaps unduly high (Table 26).

*Other Diseases.*—A study of the disease prevalent in affected towns coincident with infantile paralysis showed nothing of importance. A further study of recent antecedent illnesses in the patient showed merely a number of minor ailments of no especial significance (Table 27).

*Diet.* — The relation of diet to infantile paralysis possibly is of great importance, but as yet no definite relation between the disease and certain kinds of food has ever been made out. Although evidently unusual, the disease does occur in breast-fed babies, four cases of the kind having been recorded in our returns of the last two years (Table 28).

TABLE 28.—DIET (1909-1910)

| | | Per cent. |
|---|---|---|
| General | 283 | 80.85 |
| (a) Raw cow's milk | 308 | 88.00 |
| (b) Condensed milk | 15 | 4.28 |
| (c) Breast milk and other food | 19 | 5.42 |
| (d) Breast milk alone | 4 | 1.14 |
| Fish | 265 | 75.71 |
| Fruit | 288 | 82.28 |
| Berries | 197 | 56.28 |
| Meat | 275 | 78.57 |
| Canned goods; (a) fruits; (b) vegetables; (c) fish | 202 | 57.71 |
| Cereals | 140 | 40.00 |
| Bread and butter | 23 | 6.57 |
| Vegetables | 275 | 78.57 |
| Stews and soups | 11 | 3.14 |
| Eggs | 186 | 53.14 |
| Tea, coffee, cocoa | 6 | 1.71 |
| Malted milk | 2 | .57 |
| Ice cream | 83 | 23.71 |
| Predigested and beef juices | 4 | 1.14 |
| Candy | 27 | 7.71 |
| Bananas | 6 | 1.71 |
| For cases numbering | 350 | ..... |

TABLE 29.—DETAILS OF DIGESTIVE DISTURBANCE (1909-1910) PRECEDING ATTACK

| | | Per cent. |
|---|---|---|
| Nausea and vomiting | 120 | 34.28 |
| Constipation | 109 | 31.14 |
| Colic | 5 | 1.42 |
| Diarrhea | 39 | 11.14 |
| Indigestion or stomach upset | 4 | 1.14 |
| Mucus in stools | 2 | .57 |

| | | |
|---|---|---|
| ACCOMPANYING ATTACK | | |
| Nausea and vomiting | 140 | 40.00 |
| Constipation | 149 | 42.57 |
| Colic | 15 | 4.28 |
| Diarrhea | 56 | 16.00 |
| Indigestion (indefinite) | 3 | .85 |
| Mucus in stools | 1 | .28 |
| FOLLOWING ATTACK | | |
| Nausea and vomiting | 5 | 1.42 |
| Constipation | 122 | 34.85 |
| Colic | 2 | .57 |
| Diarrhea | 18 | 5.14 |
| Mucus in stools | 2 | .57 |
| Data for cases numbering | 350 | ..... |

TABLE 30.—GENERAL FEATURES OF ACUTE ATTACK (1907-1910)

| | | Per cent. |
|---|---|---|
| Fever | 636 | 88.33 |
| Pain and tenderness | 528 | 73.33 |
| Brain symptoms | 266 | 36.94 |
| Retraction | 248 | 34.44 |
| Sore throat | 65 | 9.02 |
| For cases numbering | 720 | ..... |

TABLE 31.—APPEARANCE OF PARALYSIS IN DAYS AND WEEKS AFTER ONSET OF FEVER (1907-1910)

| | | Per cent. |
|---|---|---|
| Preceding attack | 2 | .33 |
| Same day | 95 | 16.12 |
| One day | 93 | 15.78 |
| Two days | 103 | 17.49 |
| Three days | 98 | 16.63 |
| Four days | 58 | 9.84 |
| Five days | 22 | 3.73 |
| Six days | 51 | 8.65 |
| Seven days | 18 | 3.05 |
| Eight days | 6 | 1.01 |
| Nine days | 2 | .33 |
| Ten days | 4 | .67 |
| Eleven days | 3 | .509 |
| Twelve days | 5 | .84 |
| Thirteen days | 1 | .169 |
| Fourteen days | 4 | .67 |
| Not known (fatal) | 1 | .169 |
| 2 to 3 weeks | 6 | 1.01 |
| 3 to 4 weeks | 1 | .169 |
| 4 to 5 weeks | 1 | .169 |
| 8 weeks | 1 | .169 |
| Two days previous | 1 | .169 |
| Not stated | 13 | 2.207 |
| Total | 589 | ..... |

*Symptoms.*—Digesaive disturbances are common before, during and after the attack. Diarrhea is less frequent, comparatively, than constipation (Table 29).

The analysis of the general symptoms of the acute attack in 720 cases show fever present in 88 per cent., brain symptoms in 37 per cent., and retraction of the head in 34 per cent. Sore throat was only recorded as present in 9 per cent. (Table 30).

*Appearance of Paralysis.*—The appearance of paralysis in relation to the attack was studied in 589 cases. In 16 per cent. paralysis occurred on the day of the attack; in 16 per cent., one day after the attack; in 17 per cent., two days after the attack and in 16 per cent., three days after the attack. That is to say, in 65 per cent., within three days after the attack. In two cases it was recorded as coming before the attack and in twenty-three cases (4 per cent.) between one and two weeks after the onset (Table 31).

*Pain and Tenderness.*—The great importance of pain and tenderness as a symptom is not sufficiently recognized; 1,198 cases were analyzed in this regard and in 70.5 per cent. these symptoms were present. The disappearance of pain and tenderness in an analysis of 604 cases, in which the time was recorded, occurred in 30 per cent. within one week, in 15 per cent. in from one to two weeks, and in 13 per cent. in from two to four weeks. In five cases it was recorded as lasting two to three months and in three cases as lasting several months (Tables 32 and 33).

TABLE 32.—PAIN AND TENDERNESS (1907-1910)

| | | Per cent. |
|---|---|---|
| No pain | 178 | 14.85 |
| Pain | 845 | 70.53 |
| Not stated | 175 | 14.6 |
| Total | 1,198 | ..... |

TABLE 33.—DISAPPEARANCE OF PAIN AND TENDERNESS (1909-1910)

| | | Per cent. |
|---|---|---|
| 1 day or less | 11 | 1.82 |
| 2 days | 22 | 3.64 |
| 3 days | 29 | 4.801 |
| 4 days | 15 | 2.48 |
| 5 days | 14 | 2.31 |
| 6 days | 3 | .496 |
| A few days | 28 | 4.63 |
| 1 week | 59 | 9.76 |
| 1-2 weeks | 91 | 15.06 |
| 2-3 weeks | 46 | 7.61 |

| | | |
|---|---|---|
| 3-4 weeks | 33 | 5.46 |
| 4-5 weeks | 1 | .16 |
| 6-7 weeks | 1 | .16 |
| 1-2 months | 28 | 4.63 |
| 2-3 months | 5 | .82 |
| Several months | 3 | .496 |
| Until death | 39 | 6.45 |
| Present when report was made. | 175 | 29.13 |
| Total | 604 | ..... |

*Distribution of Paralysis.*—The distribution of paralysis was studied in 1,158 cases. The most common location was in one leg, occurring in 28 per cent.; both legs came next in frequency with 24 per cent.; one or both arms in 9 per cent.; and where one arm and leg were affected, a hemiplegic distribution was more common than a crossed paralysis, the relative percentages being 10 per cent. and 3 per cent. Special attention should be called to the frequent occurrence of paralysis of the back, abdomen, neck and face, which are much more frequent than is supposed and too often overlooked (Table 34).

TABLE 34.—DISTRIBUTION OF PARALYSIS (1907-1910)

| | | Per cent. |
|---|---|---|
| One leg only | 324 | 27.97 |
| Both legs only | 272 | 23.48 |
| Back | 154 | 13.29 |
| Both arms and both legs | 129 | 11.13 |
| One arm and leg, same side | 110 | 9.49 |
| One arm only | 84 | 7.25 |
| Both legs and one arm | 75 | 6.47 |
| Face | 74 | 6.38 |
| Abdomen | 67 | 5.78 |
| One arm and leg, opposite sides | 33 | 2.84 |
| Respiration | 31 | 2.67 |
| Both arms only | 23 | 1.98 |
| Neck | 11 | .94 |
| Both arms and one leg | 10 | .86 |
| Deglutition | 7 | .604 |
| Neck and back | 6 | .51 |
| Ataxia (transitory) | 5 | .43 |
| General | 3 | .25 |
| Intercostal | 1 | .086 |
| Both arms, back, chest and throat | 1 | .086 |
| For cases numbering | 1,158 | ..... |

*Prognosis.*—In order to throw additional light on the question of prognosis, Dr. B. E. Wood of Boston was requested by the Board to investigate the present condition of all patients reported to the Board as paralyzed in the year 1907. This inquiry was made with especial refer-

ence to the number of recoveries occurring in the four years which had elapsed. Letters were sent to all physicians who had reported cases in 1907, asking whether or not such patients had recovered, and when recovery was reported, such cases were seen unless they had disappeared or moved, and if such was the case all available information was obtained about the patients.

Of 234 cases, twenty-two could not be investigated, eleven had died in the acute stage of the disease; eight others had died subsequently of other diseases. Although two of them are said to have recovered from the paralysis, no trace could be found of three cases. In 212 cases, therefore, the termination is known, and fifty-ceven of these (27 per cent.) are reported as having recovered.

On investigation it was found that there were three classes of recovery: (1) Complete recovery without atrophy, (2) recovery with complete function but with some atrophy, (3) recovery with some hypertrophy of the affected limb. The table shows the proportion of each of these.

TABLE 35.—CONDITION OF PATIENTS AFTER RECOVERY

| | | Per cent. |
|---|---|---|
| Complete recovery without atrophy | 16 | 28.1 |
| Functional recovery with atrophy | 21 | 36.8 |
| Recovery with some hypertrophy | 3 | 5.3 |
| Recovery, presence or absence of atrophy unknown | 17 | 29.8 |

When atrophy was present, the maximum amount noted was as follews:

TABLE 36.—REMAINING ATROPHY AFTER RECOVERY

| | |
|---|---|
| Calf | 1¾ inches |
| Thigh | 1¼ inches |
| Arm | ½ inch |
| Forearm | ¾ inch |

In most cases the atrophy was much less than this, a difference of one-eighth inch being counted as atrophy, but in all such cases function of every muscle was perfect. The amounts of hypertrophy recorded were in two instances one-fourth inch and in one, three-eighths inch, all of the calf.

In these cases the severity of the attack was classed as:

TABLE 37.—SEVERITY OF THE ATTACK

| | | Per cent. |
|---|---|---|
| Severe | 14 | 24.5 |
| Moderate | 9 | 15.9 |
| Mild | 28 | 49.1 |
| Not noted | 6 | .... |
| | 57 | .... |

The distribution of the paralysis in the fifty-seven recovered cases was as follows:

TABLE 38.—DISTRIBUTION OF THE PARALYSIS

| | |
|---|---|
| One lower extremity | 12 |
| Both lower extremities | 9 |
| One upper extremity | 6 |
| Both upper extremities | 2 |
| One lower and one upper extremity | 10 |
| Three extremities | 7 |
| Four extremities | 5 |
| Face alone | 1 |
| General | 1 |
| Not given | 4 |

In addition to this distribution, paralysis of the face also existed in four, of the back in five, of the face and back in one, and of the abdominal muscles in one.

The time of recovery in the fifty-seven cases was as follows:

TABLE 39.—TIME OF RECOVERY

| | |
|---|---|
| 1 week or less | 2 |
| 1 week to 1 month | 8 |
| 1-2 months | 8 |
| 2-3 months | 5 |
| 3-6 months | 10 |
| 6-12 months | 9 |
| 1-2 years | 5 |
| 2-3 years | 5 |
| No data | 5 |

## CONCLUSIONS AS TO PROGNOSIS

The following conclusions seem justified as regards prognosis:

1. Complete recovery or functional recovery occurs in something over 25 per cent. of patients examined at the end of four years.

2. Atrophy may exist without impairment of function.

3. In about half of the recovered patients the onset was mild.

4. The distribution of the paralysis in such cases was not essentially different from that of cases which do not recover.

5. The period of recovery in many instances occupied months, and in several cases from one to two years.

234 Marlboro Street—145 State House.

## ABSTRACT OF DISCUSSION

### ON PAPERS OF DIXON AND LOVETT AND RICHARDSON AND KARSNER

DR. PHILIP KING BROWN, San Francisco: I shall take up the subject of poliomyelitis from a different point of view, one that concerns us more particularly in the West. I have been associated with three epidemics of this disease, two of which are not on record. Besides these there have been two others in this state. In 1898, during the month of June, Dr. Newmark and I studied an epidemic of four cases that occurred in the San Joaquin Valley in the town of La Grand, with a population of but forty-nine people. One of these patients died. In 1903 Dr. Alice Wood reported twenty-five cases in and about San Francisco. In 1906 I collected eight cases in an epidemic at Watsonville, Cal., most of them seen by Dr. Saxton Pope. None of the patients died. Last year I collected twenty-five cases within a radius of a few miles at the upper end of the Sacramento Valley. Drs. Lennon, Fleischner and others collected in the neighborhood of seventy-five cases in San Francisco and vicinity last winter, and a report of this epidemic will be made next month by Dr. Fleischner.

The importance of this historically is the thing I want to mention. We have seen in California epidemics of poliomyelitis in towns quite apart, one of them far away from railway communications, two in a great center and one in a thickly-settled agricultural district. Some of these epidemics occurred in the fall and winter during the rainy season and some in the summer months when no rain falls in California. Often there is cesspool drainage in country districts and pollution of the wells occurs. We must all appreciate that this disease occurs in epidemics and that it bears a definite relation in some way to bacterial growth.

The facts that we must reconcile to-day are those presented by the readers of the first paper and those in the investigations reported from Massachusetts. The latter, together with what Dr. Simon Flexner has reported thus far, have enabled us to secure definite information regarding the type of the disease met with and certain facts regarding the organism responsible for the disease. It is quite possible that the organism referred to by the reader of the first paper may be shown to be responsible for the disease, but the failure of a large number of investigators to obtain corroborating proof must make us suspend judgment, and indicates plainly how difficult the task is of proving the connection of on organism with this disease. Flexner and Lewis, Gay and Lucas, and many others in this country and abroad, have given us valuable data about the characters of the infecting organism but no conclusive facts as to the organism itself.

The fact that we are dealing with disease at times acutely epidemic should be clear when we read the report by Müller of an undoubted epidemic that occurred in Nauru, an island in Oceania, where there appeared 700 cases among 25,000 inhabitants. He states that in three months 650 showed no paralysis whatever. That fact indicates the varying intensity of the disease as it occurs in different epidemics, for our experience in this country indicates a resulting paralysis as high as 90 per cent. in some epidemics. Doubtless Müller was able to include the abortive cases in his group, whereas they must frequently escape notice in epidemics in cities or less detached localities.

What all of us are interested in is this: It is a type of disease that is not recognized as a rule when it occurs sporadically, until the paralysis occurs. This is told us by men with an abundant experience but it should not deter us from being on the lookout for the disease at all times all over the country. The chief value of this symposium seems to me to be the knowledge of the multiform char-

acter of the disease and the help in recognizing it and dealing with it, which becomes now our common property through the efforts of these investigators.

In several cases that appeared during an epidemic in Northern California the febrile conditions lasted for ten days. I saw several patients who were brought to San Francisco still in the febrile stage. The reason for keeping the children quiet is because the destructive trouble is chiefly in the cervical and lumbar regions. The process, of course, is a diffuse myelitis and the thickest parts of the cord suffer most, probably from mechanical conditions. Activity could only increase the evil effects of these conditions.

At the last meeting of the Association of American Physicians at Atlantic City, the report of Dr. Simon Flexner of the Rockefeller Institute for Medical Research was of great interest, particularly as to what he stated with regard to the use of hexamethylenamin (urotropin) and certain allied products. He also calls attention to the great desirability of keeping the nasal mucous membrane cleansed with some mild antiseptic solution. The result is very efficacious in preventing the microorganisms from penetrating the mucous membrane or from being transmitted to others through breathing, sneezing, or coughing.

The question of diagnosis is so complicated that I do not feel like considering it; but I will say this: one must look out for evidences of the disease and one must be constantly prepared to meet it. The occurrence of coryza, acute bronchitis with fever, pain in the neck, and other early symptoms of this disease should make us careful. When such an instance is met with, we should insist on keeping the child in bed and under careful observation.

Caverly, in an epidemic that occurred in Vermont, referred to the appearance of the disease in animals. A spinal cord of a chicken was sent to Dr. Charles Dana, who satisfied himself that there was the same form of degeneration in it that occurred in the human being.

# RECOVERY OF A TYPHOID BACILLUS-CARRIER DURING VACCINE TREATMENT *

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Medical literature during the past five years has contained numerous reports of chronic typhoid bacillus-carriers, but there has been very little discussion of the treatment of these patients. The reason for this paucity appears to be that treatment has been unsatisfactory, and in but few cases has the infection been eradicated.

Dehler[1] has cured by cholecystostomy two patients who discharged the bacilli in the feces, but the bacilli did not disappear from the stools of a paratyphoid carrier on whom Forster[2] did cholecystostomy for gallstones. Grimme[3] reported the recovery of an intestinal typhoid carrier on whom cholecystectomy was done. Park[4] failed to eradicate the infection in "Typhoid Mary," an intestinal carrier, by the use of intestinal antiseptics and hexamethylenamin; the latter drug was given in doses of 100 to 150 grains daily. Park cites Lentz, who stated that he could not get rid of the bacilli by any treatment. Albert[5] reported the disappearance of bacilli from the urine of a carrier treated with hexamethylenamin, but no details were given and no statement made as to permanent recovery. Niepraschk[6] had success with hexamethylenamin and boric acid (triborate of hexamethylentetramin) in the treatment of a urinary carrier after he had failed with hexamethylenamin alone and in combination with resorcin. He gave this preparation in doses of 1.5 gm. four times daily. Hammond[7] failed to cure an intestinal carrier to whom he gave hexamethylenamin for months.

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*From the Medical Clinic of Colon Hospital, Cristobal, Canal Zone.

1. Dehler: München. med. Wchnschr., 1907, liv, No. 43.
2. Forster: Verhandl. d. deutsch. path. Gesellsch., 1907, p. 163.
3. Grimme: München. med. Wchnschr., 1908, lv, No. 1.
4. Park, W. H.: Jour. Am. Med. Assn., 1908, li, 981.
5. Albert, H.: Jour. Am. Med. Assn., 1908, li, 982. Discussion of Dr. Park's paper.
6. Niepraschk: Ztschr. f. Hyg. u. Infektionskrankh., 1909, lxiv, 454.
7. Hammond, F. S.: Jour. Am. Med. Assn., 1909, lii, 48.

LV

Litterer[8] treated by vaccination a patient with a discharging typhoid bone lesion. He estimated that there were a half million bacilli in a platinum loopful of the pus. He thought, justifiably, that the patient should be regarded as a chronic typhoid bacillus-carrier. Under vaccine treatment the patient showed great improvement, but was not entirely cured at the time of the report. He has recently informed us that this patient and another similar carrier were both cured by vaccination in three and two months, respectively.

Irwin and Houston[9] have successfully treated a urinary carrier by vaccination after failure with hexamethylenamin. The bacilli disappeared after the third dose and four subsequent examinations covering a period of two months were negative. Six vaccinations were given, the doses increasing from 50 to 1,000 million. Meader[10] treated successfully by vaccination a patient who discharged bacilli in her feces. The patient had had typhoid fever thirty years previously and had been exposed to infection five years previously. Before vaccination was begun, treatment was attempted with hexamethylenamin; 15 grains three times daily for two weeks were given, and then 75 grains daily. The large doses had to be discontinued after three or four days because of painful micturition. No diminution in the number of typhoid bacilli discharged in the feces could be detected. An attempt was then made to plant *B. coli* in the lower bowel in the hope that it would overgrow the typhoid organisms. Four doses, each about a pint, of a bouillon culture, were given per rectum. The typhoid organisms persisted in the stools and treatment with lactic acid bacillus tablets was tried; this also failed. Autogenous vaccines were then given at intervals of from one to two weeks. Six vaccinations were given, the doses increasing from 25 to 1,000 million, after which the stool cultures were negative on three separate examinations. Meader studied the bactericidal and agglutinating power of the blood during vaccination. The former rapidly rose, reaching its greatest power after 400 million bacilli were injected; it then fell rapidly, and seven days after 1,000 million bacilli were injected the bactericidal power had fallen to a point practically the same as when immunization work began. An interesting observation was that during the period of declining bacteri-

8. Litterer, W. L.: Jour. Am. Med. Assn., 1908, li, 982. Discussion of Dr. Park's paper.

9. Irwin, S. T., and Houston, T.: Lancet, London, Jan. 30, 1909.

10. Meader, F. M.: Bull. Johns Hopkins Hosp., 1910, xxi, 280.

cidal power the agglutinating power became evident in dilutions of from 1 to 500 in one hour. The first stool examination that was found negative was seven days after the above phenomenon. No examination was made for twenty-three days previously, so it is difficult to correlate the disappearance of the bacilli with the serum phenomena. Meader seems inclined to think that the high bactericidal power of the serum was immediately correlated with the disappearance of the bacilli, but the stool was positive for bacilli only three days before the examination that showed the highest point of bactericidal power, and ten days after the previous examination. The bacilli disappeared some time during a period of twenty-three days that covered the maximum point and the rapid decline of bactericidal power and the rise and fall of agglutinating power. Our experience with our own case leads us to suggest that the phenomena were coincidences, and that the disappearance of bacilli was due to the healing of a chronic lesion under the influence of vaccination — that the healing was completed coincidentally with the serum phenomena.

Cummins, Fawcus and Kennedy[11] treated six typhoid carriers and one paratyphoid A carrier. Two of these were urinary carriers and five intestinal. They used implantation of *B. bulgaricus;* they tried intestinal and urinary antiseptics, including hexamethylenamin (urotropin) alone and together with another diuretic; they attempted to influence the infection by acidifying the urine by means of the administration of sodium benzoate and acid phosphate of soda; they exposed the gall-bladder and kidneys to *x*-rays; and they vaccinated three patients with stock and autogenous vaccines.

One intestinal carrier recovered during the administration of *B. bulgaricus* in large doses, but others were not improved by it. An intermittent intestinal carrier ceased to discharge bacilli on two occasions after exposure of the gall-bladder to the *x*-rays, and the bacilli were not found in his stools when he was discharged from observation. It was thought, however, that this absence of bacilli might be due to a natural intermission rather than to cure by treatment. Bacilli in the feces and urine respectively of two other patients decreased in numbers after *x*-ray treatment, but increased again when treatment was discontinued. Antiseptics reduced the number of bacilli but when antiseptics were discontinued the number rapidly rose. Vaccination was carried out on three patients,

11. Cummins, S. L.: Fawcus, H. B., and Kennedy, J. C.: Treatment of Typhoid Carriers, Jour. Roy. Army Med. Corps, Lond., 1910, xiv, 351.

TABULATED DATA

| Date. | Vaccin. Millions of Bacilli | Stool Cultures | Urine Cultures | Colonies per Loopful | Loopfuls of Urine Used | Agglutination Tests | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Stock Culture | | | Urine Culture | | |
| | | | | | | Dilution Serum | Reaction | Time (hrs.) | Dilution Serum | Reaction | Time (hrs.) |
| 9/22/10 | .... | — | — | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 10/4/10 | .... | — | .. | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 10/7/10 | .... | — | + | +† | ..... | 1-40 | ± | 1 | 1-40 | + | 1 |
| 10/10/10 | 25 | .. | .. | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 10/11/10 | .... | — | .. | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 10/15/10 | .... | .. | + | +† | ..... | 1-50 | ± | 1 | 1-40 | ± | 1 |
| 10/19/10 | 50 | .. | .. | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 10/26/10 | .... | .. | + | +† | ..... | 1-50 | — | 1 | 1-50 | + | 1 |
| 10/28/10 | 100 | .. | .. | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 11/4/10 | .... | .. | + | +† | ..... | 1-50<br>1-100 | +<br>+ | 1<br>6 | ..... | .. | .. |
| 11/6/10 | 150 | .. | .. | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 11/16/10 | 200 | .. | + | +† | ..... | 1-50<br>1-200 | +<br>+ | 1<br>2 | ..... | .. | .. |
| 11/26/10 | 250 | .. | + | 92 | 3 | 1-100<br>1-250 | +<br>+ | 1<br>2 | ..... | .. | .. |
| 2/6/10 | 400 | .. | + | 18 | 3 | 1-500 | + | 3 | ..... | .. | .. |
| 12/9/10 | .... | .. | + | 45 | 3 | ..... | .. | .. | 1-50<br>1-200<br>1-300 | +<br>++<br>± | 1<br>2<br>2 |
| 12/17/10 | .... | .. | + | 32 | 3 | 1-150<br>1-1000 | +<br>+ | 1<br>6 | 1-150<br>1-300<br>1-400 | —<br>+<br>± | 1<br>6<br>6 |
| 1/3/11 | .... | .. | + | 5 | 3 | 1-150<br>1-200 | +<br>± | 6<br>6 | 1-150<br>1-200 | +<br>— | 6<br>6 |
| 1/10/11 | 1000 | .. | .. | ... | ..... | ..... | .. | .. | 1-50 | + | 1 |
| 1/21/11 | .... | .. | + | 2 | 3 | 1-150 | ± | ..<br>1 | 1-150<br>1-200 | +<br>± | 1<br>1 |
| 2/1/11 | 1500 | .. | .. | ... | ..... | ..... | .. | .. | ..... | .. | .. |
| 2/11/11 | .... | .. | ? | ... | 3 | 1-400 | + | 5 | 1-400 | + | 5 |
| 2/15/11 | .... | .. | — | 0 | 3 | 1-1000 | + | 6 | 1-1000 | + | 6 |
| 2/20/11 | .... | .. | — | 0 | 0.2 c.c. | ..... | .. | .. | ..... | .. | .. |
| 2/28/11 | .... | .. | — | 0 | 0.2 c.c. | ..... | .. | .. | ..... | .. | .. |
| 3/1/11 | .... | .. | .. | ... | ..... | 1-1000 | + | 6 | 1-600<br>1-1000 | +<br>± | 6<br>6 |
| 3/24/11 | .... | .. | — | 0 | 2 c.c.§ | 1-200<br>1-400<br>1-800 | +<br>+<br>— | 1<br>4<br>19 | ..... | .. | .. |
| 5/2/11 | .... | .. | — | 0 | 10 c.c.§ | ..... | .. | .. | ..... | .. | .. |

* Forty typhoid-like colonies per loopful of urine. A transplant from one colony proved it to be *B. fecalis alkaligenes*. Colonies of *B. coli* were also present. We thought it probable that all the colonies were contaminations and decided to make other cultures from a more carefully obtained urine.

† Numerous. § Bouillon inoculated and plates made from bouillon cultures.

one an intestinal carrier, two urinary carriers. It failed in all three cases to eradicate the infection.

The authors are sure, therefore, of the recovery of only one patient during treatment, an intestinal carrier treated with lactic acid bacilli (*B. bulgaricus*). They think that a combination of vaccination with hexamethylenamin in urinary carriers, and of vaccination with *x*-rays in gall-bladder intestinal carriers may prove to be effectual.

Stone[12] has reported one typhoid carrier treated by vaccination. His patient was a urinary carrier, and recovered during treatment with autogenous vaccines. Six doses, increasing from 100 to 400 million, were given, and stool cultures were negative after the sixth dose.

To sum up, three chronic intestinal typhoid carriers have recovered after operations on the gall-bladder. One urinary carrier has recovered during the administration of hexamethylenamin in combination with boric acid (triborate of hexamethylentetramin). One intestinal carrier recovered when lactic acid bacilli (*B. bulgaricus*) were implanted in the alimentary tract. One intestinal carrier apparently recovered after repeated exposures of the gall-bladder to *x*-rays. One intestinal carrier, two urinary carriers, and two carriers discharging bacilli from bone lesions have recovered during vaccination with autogenous vaccines. We shall add to the number one urinary carrier that recovered likewise during vaccination with autogenous vaccine. Altogether then, there have been only twelve recoveries of typhoid carriers as far as we have been able to find; six recoveries of intestinal carriers, four of urinary carriers and two of carriers with bone lesions. Including our own patient, six have recovered during treatment with autogenous vaccines.

### CASE REPORT

Our patient was a little American girl, white, aged 4½ years. She had had an attack of fever, that was probably a mild initial attack of typhoid, in July, 1910, during which she was not under our care. She was admitted to Colon Hospital (No. 26,236) Aug. 3, 1910. She had a typical uneventful rather mild attack of typhoid fever, during which her serum in 1 to 50 dilution agglutinated the stock culture of *B. typhosus* in one hour. During the last fourteen days of convalescence she was given for prophylactic reasons 3 grains of hexamethylenamin three times daily—rather large doses for a small child. She was discharged from the hospital Sept. 3, 1910.

On September 18, the child's mother was admitted to the hospital with continued fever, the onset having been about three days previously, or twelve days

12. Stone, W. J.: Jour. Am. Med. Assn., 1910, lv, 1708.

after the child's return home. *B. typhosus* was isolated by blood culture. The course of illness was typical of a rather severe attack of typhoid fever.

On September 19, the child's father was admitted with a mild remittent fever that persisted ten days, maximum 101.5 F. The onset of his attack was September 16, or thirteen days after the child's return home. A blood-culture, made after six days of fever and four days before the temperature remained normal, was negative. Although the patient had never had typhoid fever, two agglutination tests by Bass'[13] macroscopic method were positive. There appeared a few quite definite rose spots. The spleen was not palpable. In the light of these facts and of subsequent events, it is quite certain that this was a mild attack of typhoid fever.

These two cases led us at once to suspect that the child was discharging typhoid bacilli in her urine or feces, and that she had infected her father and mother. Four examinations of her stools were all negative for *B. typhosus*. On the first attempt we failed, also, to obtain *B. typhosus* from the urine, but the second culture, Oct. 7, 1910, was positive, and the organisms were isolated ten times thereafter without a failure until they finally disappeared, Feb. 15, 1911, about six months after the attack of typhoid fever was over. Five successive negative examinations, covering a period of about three months, were then made.

Vaccination with autogenous vaccines was begun on Oct. 10, 1910, and nine doses, increasing from 25 to 1,500 million, were given, the last on Feb. 1, 1911, after which typhoid bacilli could no longer be isolated from the urine. The bacilli gradually decreased in numbers as vaccination proceeded. The first vaccine used (seven doses) was sterilized at 60 C. for one hour; the second vaccine (two doses), at 53 C. for one hour. The vaccinations gave slight local reactions only until the last injection of 1,500 million bacilli, when a mild general reaction occurred. The injection was given about 10 a. m., February 1, and at 8 p. m. the patient's temperature was 102. By noon the next day, the temperature had reached normal. During the entire time the patient seemed in perfect health.

Numerous agglutination tests were made before, during and following the vaccination period. Before vaccination the patient's serum in a 1-to-40 dilution gave a positive reaction in one hour against a suspension in salt solution of a twenty-four-hour agar culture of her own organisms, and an incomplete reaction against the bacilli of a stock culture. Three days after the first vaccination the reaction against both strains was incomplete. Seven days after the second vaccination, a 1-to-50 dilution of serum agglutinated the urine culture in one hour, but the reaction was negative in one hour against the stock culture, which, however, was agglutined in six hours by dilutions of serum up to 1 to 200. After the seventh vaccination (400 million bacilli), the serum in a 1-to-150 dilution agglutinated the stock culture in one hour, and in six hours the stock culture was agglutinated by a 1-to-1,000 dilution. At this time a 1-to-150 dilution of the serum failed to agglutinate the urine culture, and in six hours the maximum dilution that caused agglutination was 1 to 300. Vaccination was then suspended for thirty-five days, during which the agglutinating power of the serum decreased. After twenty-eight days a 1-to-150 dilution of the serum agglutinated both strains in six hours, but in the same time a 1-to-200 dilution gave an incom-

13. Bass, C. C.: The Archives Int. Med., 1910, vi, 717.

plete reaction against the stock culture and was negative against the urine culture. Vaccination was resumed Jan. 10, 1911, and on Jan. 21 a 1-to-150 dilution of serum agglutinated in one hour the urine culture, but gave an incomplete reaction against the stock culture. On Feb. 1, 1911, the last vaccination (1,500 million bacilli) was given, and on February 15 the serum in a dilution of 1 to 1,000 agglutinated both organisms in six hours. On March 1, a 1-to-1,000 dilution still agglutinated the stock culture in six hours, but the reaction was incomplete against the urine culture. On March 24, nearly two months after the last vaccination, the serum in a 1-to-200 dilution agglutinated the stock culture in one hour, and a 1-to-400 dilution, in four hours.

Between the dates of Dec. 6, 1910, and Jan. 10, 1911 (see table), no vaccinations were given, and the agglutinating power of the serum against both the urine culture and the stock culture decreased. On December 17, a 1-to-1,000 dilution of serum was positive in six hours against the stock culture, but a 1-to-300 dilution was the maximum dilution positive against the urine culture. On January 3, a 1-to-200 dilution gave in six hours an incomplete reaction against the stock culture and a negative result against the urine culture. During the period of this decreasing agglutinating power of the serum, the number of bacilli in the urine not only failed to increase, but actually decreased from 32 per loopful of urine on December 17 to 5 per loopful on January 3.

At the time of the observations no records were made of the numbers of colonies on the plates, but our impression is that during the first two months the number remained approximately the same. On November 26, there were 92 colonies per loopful of urine, and, with one exception, the number decreased gradually thereafter—92, (18), 45, 32, 5, 2, 0.

| | |
|---|---|
| Nov. 26, 1910 | 92 colonies per loopful |
| Dec. 9, 1910 (13 days' interval) | 45 colonies per loopful |
| Dec. 17, 1910 (8 days' interval) | 32 colonies per loopful |
| Jan. 3, 1911 (17 days' interval) | 5 colonies per loopful |
| Jan. 21, 1911 (18 days' interval) | 2 colonies per loopful |
| Feb. 11, 1911 (21 days' interval) | 0 colonies per loopful |

If the time intervals are all changed to two weeks and the number of bacilli are calculated for each examination according to the rate of decrease for each period, the following results are obtained: 92, 42, 20, 4, 2, 0. In other words, the decrease in the number of bacilli proceeded with almost mathematical precision, the number being reduced one-half every two weeks, excepting during the third interval, when reduction was more rapid. A part of this reduction was not associated with an increasing agglutinating power of the blood serum, but with a decreasing power; nor did the reduction cease when the agglutinating power rose again with subsequent vaccination. The phenomena suggest strongly that antibodies produced by vaccination were not acting on bacilli in the urine, but that a chronic typhoid lesion that was discharging typhoid bacilli in the urine slowly healed under the influence of vaccination, probably as the result of the action of antibodies in the lymph or exudate on the bacilli in the lesion. That there were not antibodies sufficient even to inhibit growth in the urine was shown by inoculating the sterile urine, just after the disappearance of typhoid bacilli, with typhoid organisms from both the stock and urine cultures. Both

organisms grew well, in spite of the fact that the agglutinating power of the blood serum at this time was 1 to 1,000 in six hours.

Our experience leads us to suggest, therefore, that the eradication of the infection of chronic typhoid carriers by vaccination is brought about by the gradual healing of a chronic lesion under the influence of antibodies produced by the vaccination. If the bacilli grow in secretions and excretions only, it does not seem that vaccination would be effectual. Hexamethylenamin or lactic acid bacilli might be effectual in such cases. The only other treatment that our patient received was four 5-grain doses of hexamethynamin on December 6 and 7. The previous examination of urine, November 26, had shown 92 bacilli per loopful. This result had discouraged us, and we brought the patient to the hospital to give a trial to hexamethynamin treatment. We obtained a specimen of urine and began hexamethylenamin treatment before the plates were incubated. On the following day, we found the number of colonies so reduced that we discontinued hexamethylenamin and resumed vaccine treatment. That the four doses of hexamethylenamin had no permanent effect on the bacilli was shown by the fact that the number of organisms was 45 per loopful two days after the drug was given.

There may be a question as to whether or not our patient should be considered a chronic typhoid carrier. According to the classification of Frosch,[14] she should be considered one. Frosch divided carriers into two groups: "those who excrete bacilli for less than three months, and those who excrete them for three months and longer. The latter class constitute the chronic bacilli carriers, the *Dauerausscheidern* of the Germans" (Simonds). Our patient carried typhoid bacilli for about six months after the temperature of her typhoid attack remained normal, and, accepting Frosch's classification, she may be considered fairly as having been a chronic typhoid bacillus carrier.

The possibility cannot be denied that the lesion that discharged bacilli may have undergone spontaneous healing without regard to vaccination. We prefer to say, therefore, that our patient recovered during vaccination, rather than that she was cured by the treatment. In the light of what is known of chronic typhoid carriers and of the chronicity of post-typhoid lesions, however, it does not seem probable that recovery was spontaneous.

One other objection might be made. Some typhoid carriers, both urinary and intestinal, discharge the bacilli intermittently. It may be suggested with reason that the disappearance of bacilli in our case may have been due to an intermission. This is possible. But the bacilli were present on eleven successive examinations covering a period of more than

14. Frosch: Klin. Jahrb., 1908, xix, 537. Cited by Simonds, J. P.: Am. Jour. Med. Sc., Aug., 1910, cxl, 247.

three months, they gradually decreased in numbers and finally disappeared, and they have been absent on five successive examinations covering a period of almost three months. The first urine examination made was negative for typhoid bacilli, but the result was probably due to faulty technic, for we had just begun making bacteriological examinations of stools and urines. It seems probable to us, therefore, that our patient was a continuous chronic typhoid carrier, and that she made a permanent recovery during treatment with autogenous vaccines.

### BACTERIOLOGICAL CONSIDERATIONS

*Isolation.*—The method of isolation of typhoid bacilli from the urine was that of Endo.[15] Endo's medium is a heavy agar to which is added basic fuchsin, lactose and sufficient sodium sulphite to decolorize the fuchsin. The red dye, fuchsin ($C_{20}H_{19}N_3HCl$), is an acid salt of rosanilin, a colorless leukobase. The acid component of the red rosanilin salt is easily reduced by sodium sulphite. When lactose-fermenting organisms grow on the above medium, the acid formed combines with the decolorized rosanilin and the colonies are stained red. The heavy agar medium is exactly like "ordinary" agar, excepting that 20 gm. of agar-agar per 1,000 c.c. are used instead of 15 gm. To 1,000 c.c. of the agar medium are added: lactose, 10 gm.; basic fuchsin, 1.8 c.c. of a 10 per cent. solution in alcohol; sodium sulphite, 25 to 40 c.c. of a 10 per cent. aqueous solution. The sodium sulphite should be added until the red color has changed to a faint pink. The agar medium can be prepared in bulk to be kept in stock, but the fuchsin, lactose and sodium sulphite should be added just before pouring into the plates. One hundred cubic centimeters of the medium will make about four or five plates, which should be 12 to 15 cm. in diameter. The plates are exposed to the air (covered with clean paper), for one hour, during which they harden and dry. One loopful or more of the material to be examined is then placed on the surface of the first plate, and with a sterile bent glass rod it is spread widely over the surface; the rod is then stroked over the surface of the second plate; then the third, and so on. The plates are covered, wrapped in paper to exclude light, and incubated for twenty-four hours. The colonies of the lactose-fermenting organisms are then red, while

15. Endo: Centralbl. f. Bakteriol., 1904, xxxv, 109. A transcription of Endo's article was kindly given us by Dr. S. T. Darling, chief of the Board of Health Laboratory, Ancon, Canal Zone.

the colonies of non-lactose-fermenting organisms are colorless. The method thus furnishes an easy way of isolating typhoid, paratyphoid and dysentery bacilli. The organism that causes difficulty most frequently is *B. fecalis alkaligenes.*

*Identification.*—The organisms that we isolated from the urine were small, actively motile, Gram-negative bacilli. They formed small, 1 to 2 mm. diameter, translucent colonies with a bluish refractility on agar plates. Litmus milk was slightly acidified by them and remained acid. There was an invisible growth on potato. No indol was formed in Dunham's peptone medium. Bouillon showed a general turbidity without pellicle or sediment. There was no gas formation in any of the semi-solid litmus sugar media; acid formed in dextrose, mannite, galactose and dextrin; there was no change in lactose, saccharose or dulcite. The organisms were agglutinated by the serum of a typhoid patient (the child's mother) in a 1-to-50 dilution in one hour. After the child was vaccinated with her own organisms, her serum agglutinated a stock culture of typhoid bacilli in a 1-to-200 dilution in one hour and in a 1-to-1,000 dilution in six hours.

## SUMMARY

1. The literature of the treatment of typhoid bacillus-carriers is reviewed. Eleven recoveries, excluding our case, have occurred. Five of these patients recovered during vaccination with autogenous vaccines.

2. Our patient was a white child, female, aged 4½ years. Shortly after her attack of typhoid fever, her father and mother were infected. Typhoid organisms in pure culture were isolated from the child's urine. Hexamethylenamin had been aministered to the patient during two weeks of convalescence from the typhoid attack.

3. Practically the only treatment given was vaccination with autogenous vaccines. Nine doses were given, increasing from 25 to 1,500 million. The bacilli decreased gradually and disappeared after the ninth vaccination. Eleven successive urine cultures were positive for *B. typhosus* and then five successive cultures were negative.

4. The total duration of the bacilluria, from the time of normal temperature, was about six months. The patient appeared to be a continuous carrier.

5. It seems that the disappearance of the bacilli was not an intermission but a true recovery, brought about by the gradual healing of a chronic lesion under the influence of vaccination.

We wish to thank Col. W. C. Gorgas, Chief Sanitary Officer, for permission to publish this report.

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## ABSTRACT OF DISCUSSION

DR. FRANK BILLINGS, Chicago: This is an important subject from many points of view. It demonstrates the fact that we have typhoid carriers, and that they are sources of epidemics which otherwise would not be recognized. Many of these typhoid carriers occur in individuals who give no history of ever having had typhoid fever. They may have had a cholecystitis, or a cholecystitis calculosa. It was only within the past three years that I have met with such patients. One was a woman, aged 44; she denied having suffered from anything that could be considered typhoid fever. Her blood reacted positively to the Widal test and the feces showed pure culture of the typhoid bacilli. She had suffered for some time from a chronic calculous cholecystitis and was operated on; in the gall-bladder were found stones and living typhoid bacilli.

Recently on the western coast of Florida there occurred an epidemic of typhoid fever which was due to a typhoid carrier who worked in a dairy. The first shipment of cream resulted in the production of typhoid fever in several of the guests who resided at this particular hotel. When the shipments were discontinued no new cases occurred. There were many cases of typhoid fever—and four of these were Chicagoans—as the result of this shipment. These patients ran the ordinary course of typhoid fever. To this resort was sent a member of the faculty of Rush Medical College and he traced the infection, discovering a typhoid carrier. These facts are important in showing that we should be more alert on looking for such cases. There is, also, a lesson to be learned—that we should not turn patients out from the hospitals because they appear to suffer from no symptoms of this disease; we should first look carefully into the condition of the urine and the feces. I have not been very successful in the treatment of these patients by the employment of hexamethylenamin (urotropin) even in large doses, 120 gr. per diem. Such doses certainly do have some beneficial effect on the bacilluria. The effect of this agent on the contents of the intestinal canal cannot, however, be relied on.

With regard to vaccination, it seems to me that this is a most valuable adjunct. There are some patients who give a history of having had typhoid fever; such individuals may have been typhoid carriers for years, although there are no apparent lesions in the intestines, the infection still goes on. Again, it should be remembered that the gall-bladder may be the sole focus of infection; just why the bacilli should inhabit this part of the intestinal canal we do not know. It seems to me that the conditions met with here simulate in a measure the conditions that arise in a chronic pneumococcemia. The pneumococci may infect the individual for months, and even for years. Vaccination in such cases will sometimes help, I believe, for a time, but not permanently. It seems to me, therefore, that a typhoid bacillus carrier is perhaps somewhat similar to one with chronic pneumococcemia. Vaccination, therefore, autogenenous or other, continued

for a sufficient length of time, appears to be the best remedy we have. Bacteriological examinations of the urine and feces should be more often made and reported on. Attention should be paid to the fact that these typhoid carriers are more common than is suspected.

DR. P. M. ASHBURN, U. S. Army: I am surprised to learn that only nine recovered typhoid carriers have been reported, and therefore think it worth while to report another, a case occurring in my own service. The patient was a sergeant of the Fifth Field Artillery, who had typhoid at Vancouver Barracks in October, 1909. Typhoid bacilli were found in the stools thereafter. He was transferred to the Army General Hospital at San Francisco, where weekly examination of the stools showed large numbers of typhoid bacilli, at times in almost pure cultures. He was treated with autogenous vaccines and *x*-ray exposures from November, 1909, to April, 1910, without effect. In April the *x*-ray treatment was stopped and the patient was given 1 gm. doses of sodium salicylate every four hours. After taking this for about two weeks, he was relieved of his former symptoms (pain and tenderness in the gall-bladder region), but complained of palpitation. There were still typhoid bacilli in the stools but the number had diminished. The sodium salicylate was then stopped but the decrease in typhoid bacilli continued. By the end of May, 1910, the stools were free from them and weekly examinations for six weeks thereafter showed that they remained free. The man was then sent to duty. The recovery was apparently related to the taking of the sodium salicylate.

DR. WILLIAM LITTERER, Nashville, Tenn.: Vaccination in certain cases has, I believe, a remarkable effect. I agree with Drs. Brem and Watson that it has a healing effect; this is shown in the way it acts in decreasing the number of bacilli after the first injection. In one of my cases the first loopful of pus from the wound showed the presence of over 1,000 typhoid bacilli in pure culture; in fact, there were so many that they could be counted only with difficulty. The second injection of the vaccine showed about one-half the number of typhoid bacilli. After repeated injections the number of bacilli slowly decreased. The patient was finally cured. In the other case there was a staphylococcus associated with the typhoid bacillus. I have at the present time three typhoid carriers of the intestinal type in whom I am instituting the vaccine treatment, using autogenous vaccines. I have been treating one for three months without any very marked success. The bacilli in the stools have not materially diminished, although the agglutination has been increased from 1 to 50 before the injection to 1 to 500 at the present time. The other two cases of intestinal carriers have been treated only three weeks and as yet no definite results have been obtained.

DR. WALTER BREM, Los Angeles: Dr. Frank Billings has referred to the part played by antibodies in the recovery of the patient. My own idea is that the infection was not influenced by the elimination of antibodies in the urine. The fact that typhoid bacilli grew well when inoculated into the urine after recovery of the patient when the agglutinating power of the patient's serum was 1 to 1,000, indicates that antibodies were not eliminated in the urine to any appreciable extent. The phenomena seem to indicate the presence in the urinary tract of a chronic typhoid lesion which healed gradually under the influence of vaccination. This influence was exerted presumably through the increased production of antibodies. It seems quite conceivable that before vaccination the antibodies in the scant blood and lymph-supply of a chronic lesion were not in sufficient concentration to affect the organisms, but when the blood became rich in antibodies even a

poor blood-supply could bring them in sufficient numbers to destroy the bacilli. This effect would be greatest, of course, at the margins and deepest portions of the lesion where the flow of blood and lymph would be greatest, and so a gradual healing of the lesion might occur, the area in which the bacilli were multiplying becoming smaller and smaller, thus discharging fewer and fewer bacilli into the urine. I think that this conception of a chronic lesion accounts best for the phenomena observed. The visible post-typhoid bone lesions treated by vaccination by Dr. Litterer would probably have produced just such phenomena during healing had they been present in the urinary tract.

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